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Description

A CRYSTALLINE FORM OF THE SALT OF 4-(3-CHLORO-4-(CYCLOPROPYLAMINOCARBONYL)AMINOPHENOXY)-7-METHOXY-6-QUINOLINECARBOXAMIDE OR THE SOLVATE OF THE SALT AND A PROCESS FOR PREPARING THE SAME

Technical Field

[0001] The present invention relates to a crystalline form of the salt of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide or the solvate of the salt and a process for preparing the same.

Background Art

[0002] 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (additional name: 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide) is known to exhibit an excellent angiogenesis inhibition as a free-form product, as described in Example 368 of Patent Document 1. 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide is also known to exhibit a strong inhibitory action for c-Kit kinase (Non-Patent Document 1, Patent Document 2).

However, there has been a long-felt need for the provision of a c-Kit kinase inhibitor or angiogenesis inhibitor that has high usability as a medicament and superior characteristics in terms of physical properties and pharmacokinetics in comparison with the free-form product of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide.

[0003]

[Patent Document 1] WO 02/32872

[Patent Document 2] WO 2004/080462

[Non-Patent Document 1] 95th Annual Meeting Proceedings, AACR (American Association for Cancer Research), Volume 45, Page 1070-1071, 2004

Disclosure of the Invention

Problems to be Solved by the Invention

[0004] It is an object of the present invention to provide a crystalline form of the salt of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide or the solvate of the salt which has high usability as a medicament and a process for preparing the same.

Means for Solving the Problems

[0005] In order to achieve the above object, the present invention provides the followings:

<1> A crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide, wherein said crystalline compound is the hydrochloride of said compound, the hydrobromide of said compound, the p-toluenesulfonate of said compound, the sulfate of said compound, the methanesulfonate of said compound or the ethanesulfonate of said compound, or the solvate of said salt;

<2> A crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate or the solvate of said salt;

<3> A crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide ethanesulfonate or the solvate of said salt;

<4> A crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate;

<5> A crystalline form of the hydrate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate;

<6> A crystalline form of the dimethyl sulfoxide solvate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate;

<7> A crystalline form of the acetic acid solvate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate;

<8> A crystalline form of 4-(3-chloro-4-

(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide ethanesulfonate;

<9> A crystalline form of the dimethyl sulfoxide solvate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide ethanesulfonate;

<10> A crystalline form according to <4> (Form A) having diffraction peaks at diffraction angles ($2\theta \pm 0.2°$) of 9.65° and 18.37° in a powder X-ray diffraction;

<11> A crystalline form according to <4> (Form A) having peaks at chemical shifts of about 162.4 ppm, about 128.0 ppm, about 102.3 ppm and about 9.9 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum;

<11-1> A crystalline form according to <4> (Form A) having a peak at a chemical shift of about 162.4 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum;

<11-2> A crystalline form according to <4> (Form A) having a peak at a chemical shift of about 128.0 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum;

<11-3> A crystalline form according to <4> (Form A) having a peak at a chemical shift of about 102.3 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum;

<11-4> A crystalline form according to <4> (Form A) having a peak at a chemical shift of about 9.9 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum;

<12> A crystalline form according to <4> (Form A) having absorption bands at wavenumbers of $1161 \pm 1\ cm^{-1}$ and $1044 \pm 1\ cm^{-1}$ in an infrared absorption spectrum;

<12-1> A crystalline form according to <4> (Form A) having an absorption band at a wavenumber of $1161 \pm 1\ cm^{-1}$ in an infrared absorption spectrum;

<12-2> A crystalline form according to <4> (Form A) having an absorption band at a wavenumber of $1044 \pm 1\ cm^{-1}$ in an infrared absorption spectrum;

<13> A crystalline form according to <4> (Form B) having diffraction peaks at diffraction angles ($2\theta \pm 0.2°$) of 5.72° and 13.84° in a powder X-ray diffraction;

<14> A crystalline form according to <4> (Form B) having absorption bands at wavenumbers of 1068 ± 1 cm^{-1} and 918 ± 1 cm^{-1} in an infrared absorption spectrum;
<14-1> A crystalline form according to <4> (Form B) having an absorption band at a wavenumber of 1068 ± 1 cm^{-1} in an infrared absorption spectrum;
<14-2> A crystalline form according to <4> (Form B) having an absorption band at a wavenumber of 918 ± 1 cm^{-1} in an infrared absorption spectrum;
<15> A crystalline form according to <4> (Form C) having diffraction peaks at diffraction angles (2θ ± 0.2°) of 14.20° and 17.59° in a powder X-ray diffraction;
<16> A crystalline form according to <4> (Form C) having peaks at chemical shifts of about 160.2 ppm, about 126.6 ppm, about 105.6 ppm and about 7.8 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum;
<16-1> A crystalline form according to <4> (Form C) having a peak at a chemical shift of about 160.2 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum;
<16-2> A crystalline form according to <4> (Form C) having a peak at a chemical shift of about 126.6 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum;
<16-3> A crystalline form according to <4> (Form C) having a peak at a chemical shift of about 105.6 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum;
<16-4> A crystalline form according to <4> (Form C) having a peak at a chemical shift of about 7.8 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum;
<17> A crystalline form according to <4> (Form C) having absorption bands at wavenumbers of 1324 ± 1 cm^{-1} and 579 ± 1 cm^{-1} in an infrared absorption spectrum;
<17-1> A crystalline form according to <4> (Form C) having an absorption band at a wavenumber of 1324 ± 1 cm^{-1} in an infrared absorption spectrum;
<17-2> A crystalline form according to <4> (Form C) having an absorption band at a wavenumber of 579 ± 1 cm^{-1} in an infrared absorption spectrum;
<18> A crystalline form according to <5> (Form F) having diffraction

peaks at diffraction angles ($2\theta \pm 0.2°$) of 8.02° and 18.14° in a powder X-ray diffraction;

<19> A crystalline form according to <7> (Form I) having diffraction peaks at diffraction angles ($2\theta \pm 0.2°$) of 9.36° and 12.40° in a powder X-ray diffraction;

<20> A crystalline form according to <7> (Form I) having absorption bands at wavenumbers of 1750 ± 1 cm^{-1} and 1224 ± 1 cm^{-1} in an infrared absorption spectrum;

<20-1> A crystalline form according to <7> (Form I) having an absorption band at a wavenumber of 1750 ± 1 cm^{-1} in an infrared absorption spectrum;

<20-2> A crystalline form according to <7> (Form I) having an absorption band at a wavenumber of 1224 ± 1 cm^{-1} in an infrared absorption spectrum;

<21> A crystalline form according to <8> (Form α) having diffraction peaks at diffraction angles ($2\theta \pm 0.2°$) of 15.70° and 17.18° in a powder X-ray diffraction;

<22> A crystalline form according to <8> (Form α) having absorption bands at wavenumbers of 1320 ± 1 cm^{-1} and 997 ± 1 cm^{-1} in an infrared absorption spectrum;

<22-1> A crystalline form according to <8> (Form α) having an absorption band at a wavenumber of 1320 ± 1 cm^{-1} in an infrared absorption spectrum;

<22-2> A crystalline form according to <8> (Form α) having an absorption band at a wavenumber of 997 ± 1 cm^{-1} in an infrared absorption spectrum;

<23> A crystalline form according to <8> (Form β) having diffraction peaks at diffraction angles ($2\theta \pm 0.2°$) of 6.48° and 9.58° in a powder X-ray diffraction;

<24> A crystalline form according to <8> (Form β) having absorption bands at wavenumbers of 1281 ± 1 cm^{-1} and 985 ± 1 cm^{-1} in an infrared absorption spectrum;

<24-1> A crystalline form according to <8> (Form β) having an absorption band at a wavenumber of 1281 ± 1 cm^{-1} in an infrared absorption spectrum;

<24-2> A crystalline form according to <8> (Form β) having an absorption band at a wavenumber of 985 ± 1 cm^{-1} in an infrared absorption spectrum;

<25> A process for preparing a crystalline form of 4-(3-chloro-4-

(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate (Form A), comprising a step of mixing 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide, a solvent and methanesulfonic acid to dissolve;

<25-1> A process according to <25>, wherein the solvent is methanol, ethanol or 2-propanol;

<26> A process for preparing a crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate (Form A), comprising a step of mixing 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide, acetic acid and methanesulfonic acid to dissolve;

<26-1> A process according to <26>, further comprising a step of adding a poor solvent to the mixture;

<26-2> A process according to <26-1>, wherein the poor solvent is methanol or ethanol;

<27> A process for preparing a crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate (Form B), comprising a step of drying a crystalline form of the acetic acid solvate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate (Form I) to remove acetic acid;

<28> A process for preparing a crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate (Form C), comprising a step of heating a crystalline form of the dimethyl sulfoxide solvate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate;

<29> A process for preparing a crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate (Form C), comprising a step of mixing a crystalline form of the acetic acid solvate of 4-(3-chloro-4-

(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate (Form I) and a solvent;

<29-1> A process according to <29>, wherein the solvent is methanol, ethanol or 2-propanol;

<30> A process for preparing a crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-methoxy-6-quinolinecarboxamide methanesulfonate (Form C), comprising a step of mixing 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide, acetic acid and methanesulfonic acid to dissolve;

<30-1> A process according to <30>, further comprising a step of adding a poor solvent to the mixture;

<30-2> A process according to <30-1>, wherein the poor solvent is 2-propanol;

<31> A process for preparing a crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate (Form C), comprising a step of humidifying a crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate (Form B);

<32> A process for preparing a crystalline form of the hydrate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate (Form F), comprising a step of mixing 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide, acetic acid and methanesulfonic acid to dissolve;

<32-1> A process according to <32>, further comprising a step of adding a poor solvent to the mixture;

<32-2> A process according to <32-1>, wherein the poor solvent is ethyl acetate or isopropyl acetate;

<33> A process for preparing a crystalline form of the acetic acid solvate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate (Form I), comprising a step of

mixing 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide, acetic acid and methanesulfonic acid to dissolve;

<33-1> A process according to <33>, further comprising a step of adding a poor solvent to the mixture;

<33-2> A process according to <33-1>, wherein the poor solvent is 1-propanol, 1-butanol or tert-butanol;

<34> A process for preparing a crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide ethanesulfonate (Form α), comprising a step of mixing 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide, a solvent and ethanesulfonic acid to dissolve;

<34-1> A process according to <34>, wherein the solvent is dimethyl sulfoxide;

<35> A process for preparing a crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide ethanesulfonate (Form β), comprising a step of mixing a crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide ethanesulfonate (Form α) and a solvent;

<35-1> A process according to <35>, wherein the solvent is methanol, ethanol or 2-propanol;

<36> A process for preparing a crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide ethanesulfonate (Form β), comprising a step of mixing 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide, acetic acid and ethanesulfonic acid to dissolve;

<36-1> A process according to <36>, further comprising a step of adding a poor solvent and water to the mixture;

<36-2> A process according to <36-1>, wherein the poor solvent is ethanol or 2-propanol;

<37> A pharmaceutical composition, comprising the crystalline form according to any one of <1> to <24-2>;

<38> A prophylactic or therapeutic agent for a disease for which angiogenesis inhibition is effective, comprising the crystalline form according to any one of <1> to <24-2>;

<39> An angiogenesis inhibitor, comprising the crystalline form according to any one of <1> to <24-2>;

<40> An anti-tumor agent, comprising the crystalline form according to any one of <1> to <24-2>;

<41> An anti-tumor agent according to <40>, wherein the tumor is a pancreatic cancer, a gastric cancer, a colon cancer, a breast cancer, a prostrate cancer, a lung cancer, a renal cancer, a brain tumor, a blood cancer or an ovarian cancer;

<42> A therapeutic agent for angioma, comprising the crystalline form according to any one of <1> to <24-2>;

<43> A cancer metastasis inhibitor, comprising the crystalline form according to any one of <1> to <24-2>;

<44> A therapeutic agent for retinal neovascularization, comprising the crystalline form according to any one of <1> to <24-2>;

<45> A therapeutic agent for diabetic retinopathy, comprising the crystalline form according to any one of <1> to <24-2>;

<46> A therapeutic agent for an inflammatory disease, comprising the crystalline form according to any one of <1> to <24-2>;

<47> A therapeutic agent for an inflammatory disease according to <46>, wherein the inflammatory disease is deformant arthritis, rheumatoid arthritis, psoriasis or delayed hypersensitivity reaction;

<48> A therapeutic agent for atherosclerosis, comprising the crystalline form according to any one of <1> to <24-2>;

<49> A method for preventing or treating a disease for which angiogenesis inhibition is effective, comprising administering to a patient, a pharmacologically effective dose of the crystalline form according to any one of <1> to <24-2>;

<50> Use of the crystalline form according to any one of <1> to <24-2> for

the manufacture of a prophylactic or therapeutic agent for a disease for which angiogenesis inhibition is effective;

<51> A c-Kit kinase inhibitor, comprising the crystalline form according to any one of <1> to <24-2>;

<52> An anti-cancer agent for treating a cancer expressing excessive c-Kit kinase or a mutant c-Kit kinase, comprising the crystalline form according to any one of <1> to <24-2>;

<53> An anti-cancer agent according to <52>, wherein the cancer expressing excessive c-Kit kinase or a mutant c-Kit kinase is acute myelogenous leukemia, mast cell leukemia, a small cell lung cancer, GIST, a testicular tumor, an ovarian cancer, a breast cancer, a brain tumor, neuroblastoma or a colon cancer;

<54> An anti-cancer agent according to <52>, wherein the cancer expressing excessive c-Kit kinase or a mutant c-Kit kinase is acute myelogenous leukemia, a small cell lung cancer or GIST;

<55> An anti-cancer agent according to any one of <52> to <54>, which is applied to a patient for which a cancer expressing excessive c-Kit kinase or a mutant c-Kit kinase is identified;

<56> A therapeutic agent for mastocytosis, allergy or asthma, comprising the crystalline form according to any one of <1> to <24-2>;

<57> A method for treating a cancer, comprising administering to a patient suffering from a cancer expressing excessive c-Kit kinase or a mutant c-Kit kinase, a pharmacologically effective dose of the crystalline form according to any one of <1> to <24-2>;

<58> A method according to <57>, wherein the cancer expressing excessive c-Kit kinase or a mutant c-Kit kinase is acute myelogenous leukemia, mast cell leukemia, a small cell lung cancer, GIST, a testicular tumor, an ovarian cancer, a breast cancer, a brain tumor, neuroblastoma or a colon cancer;

<59> A method according to <57>, wherein the cancer expressing excessive c-Kit kinase or a mutant c-Kit kinase is acute myelogenous leukemia, a small cell lung cancer or GIST;

<60> A method for treating a cancer, comprising the steps of:

extracting cancer cells from a patient suffering from a cancer;

confirming that the cancer cells are expressing excessive c-Kit kinase or a mutant c-Kit kinase; and

administering to the patient, a pharmacologically effective dose of the c-Kit kinase inhibitor according to <51>;

<61> A method for treating mastocytosis, allergy, or asthma, comprising administering to a patient suffering from the disease, a pharmacologically effective dose of the c-Kit kinase inhibitor according to <51>;

<62> A method for inhibiting c-Kit kinase activity, comprising applying to a cell expressing excessive c-Kit kinase or a mutant c-Kit kinase, a pharmacologically effective dose of the c-Kit kinase inhibitor according to <51>;

<63> Use of the c-Kit kinase inhibitor according to <51> for the manufacture of an anti-cancer agent for treating a cancer expressing excessive c-Kit kinase or a mutant c-Kit kinase;

<64> Use according to <63>, wherein the cancer expressing excessive c-Kit kinase or a mutant c-Kit kinase is acute myelogenous leukemia, mast cell leukemia, a small cell lung cancer, GIST, a testicular tumor, an ovarian cancer, a breast cancer, a brain tumor, neuroblastoma or a colon cancer;

<65> Use according to <63>, wherein the cancer expressing excessive c-Kit kinase or a mutant c-Kit kinase is acute myelogenous leukemia, a small cell lung cancer or GIST; and

<66> Use of the c-Kit kinase inhibitor according to <51> for the manufacture of a therapeutic agent for mastocytosis, allergy or asthma.

Effect of the Invention

[0006] A crystalline form of the salt of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (hereunder, referred to as "carboxamide") or the solvate of the salt according to the present invention has excellent characteristics in terms of physical properties (particularly, dissolution rate) and pharmacokinetics (particularly, bioavailability (BA)), and is extremely useful as an angiogenesis inhibitor or c-Kit kinase inhibitor.

Brief Description of the Drawings

[0007]

[Fig. 1] Fig. 1 is a graph illustrating the relation between time and blood concentration in a pharmacokinetic study when a crystalline form of the free form of the carboxamide, a crystalline form of the hydrobromide of the carboxamide, and a crystalline form of the methanesulfonate of the carboxamide (Form A) were administered to beagle dogs.

[Fig. 2] Fig. 2 is a figure illustrating a powder X-ray diffraction pattern for a crystalline form of the free form of the carboxamide obtained in Preparation Example 1.

[Fig. 3] Fig. 3 is a figure illustrating a powder X-ray diffraction pattern for a crystalline form of the hydrochloride of the carboxamide obtained in Example 1.

[Fig. 4] Fig. 4 is a figure illustrating a powder X-ray diffraction pattern for a crystalline form of the hydrobromide of the carboxamide obtained in Example 2.

[Fig. 5] Fig. 5 is a figure illustrating a powder X-ray diffraction pattern of a crystalline form of the p-toluenesulfonate of the carboxamide obtained in Example 3.

[Fig. 6] Fig. 6 is a figure illustrating a powder X-ray diffraction pattern for a crystalline form of the sulfate of the carboxamide obtained in Example 4.

[Fig. 7] Fig. 7 is a figure illustrating a powder X-ray diffraction pattern for a crystalline form of the methanesulfonate of the carboxamide (Form A) obtained in Example 5.

[Fig. 8] Fig. 8 is a figure illustrating a powder X-ray diffraction pattern for a crystalline form of the methanesulfonate of the carboxamide (B) obtained in Example 6.

[Fig. 9] Fig. 9 is a figure illustrating a powder X-ray diffraction pattern for a crystalline form of the methanesulfonate of the carboxamide (Form C) obtained in Example 7.

[Fig. 10] Fig. 10 is a figure illustrating a powder X-ray diffraction pattern for a crystalline form of the hydrate of the methanesulfonate of the carboxamide (Form F) obtained in Example 9.

[Fig. 11] Fig. 11 is a figure illustrating a powder X-ray diffraction

pattern for a crystalline form of the acetic acid solvate for the methanesulfonate of the carboxamide (Form I) obtained in Example 10.

[Fig. 12] Fig. 12 is a figure illustrating a powder X-ray diffraction pattern for a crystalline form of the ethanesulfonate of the carboxamide (Form α) obtained in Example 11.

[Fig. 13] Fig. 13 is a figure illustrating a powder X-ray diffraction pattern for a crystalline form of the ethanesulfonate of the carboxamide (Form β) obtained in Example 12.

[Fig. 14] Fig. 14 is a figure illustrating a ^{13}C Solid State NMR spectrum for a crystalline form of the methanesulfonate of the carboxamide (Form A) obtained in Example 5.

[Fig. 15] Fig. 15 is a figure illustrating a ^{13}C Solid State NMR spectrum for a crystalline form of the methanesulfonate of the carboxamide (Form C) obtained in Example 7.

[Fig. 16] Fig. 16 is a figure illustrating an infrared absorption spectrum for a crystalline form of the methanesulfonate of the carboxamide (Form A) obtained in Example 5.

[Fig. 17] Fig. 17 is a figure illustrating an infrared absorption spectrum for a crystalline form of the methanesulfonate of the carboxamide (Form B) obtained in Example 6.

[Fig. 18] Fig. 18 is a figure illustrating an infrared absorption spectrum for a crystalline form of the methanesulfonate of the carboxamide (Form C) obtained in Example 7.

[Fig. 19] Fig. 19 is a figure illustrating an infrared absorption spectrum for a crystalline form of the acetic acid solvate of the methanesulfonate of the carboxamide (Form I) obtained in Example 10.

[Fig. 20] Fig. 20 is a figure illustrating an infrared absorption spectrum for a crystalline form of the ethanesulfonate of the carboxamide (Form α) obtained in Example 11.

[Fig. 21] Fig. 21 is a figure illustrating an infrared absorption spectrum for a crystalline form of the ethanesulfonate of the carboxamide (Form β) obtained in Example 12.

Best Mode for Carrying Out the Invention

[0008] Hereunder, the present invention is described in detail.

[0009] As examples of the salts of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (hereunder, referred to as "carboxamide") according to the present invention, methanesulfonate, ethanesulfonate, p-toluenesulfonate, hydrochloride, hydrobromide, sulfate, tartrate and phosphate may be mentioned.

[0010] The salt of the carboxamide according to the present invention can be prepared by ordinary methods (for example, by mixing the carboxamide and the corresponding acid at a suitable ratio in the presence or absence of a solvent).

[0011] In this connection, in addition to the method described in WO 02/32872, the carboxamide can also be prepared by the method described in Preparation Examples 1 to 3 below.

[0012] As examples of the solvate of the salt of the carboxamide according to the present invention, a hydrate, a dimethyl sulfoxide solvate, an acetic acid solvate, and an *N,N*-dimethylformamide solvate may be mentioned.

[0013] In general, since an error within a range of ± 0.2° can occur for a diffraction angle (2θ) in powder X-ray diffraction, it is necessary that the above diffraction angle values are understood to also include numerical values within a range of ± 0.2° thereof. Therefore, the present invention encompasses crystals for which the diffraction angle matches within an error range of ± 0.2° in powder X-ray diffraction, as well as crystals for which the diffraction angle is completely matching in powder X-ray diffraction.

[0014] In the present specification, the phrase "having diffraction peaks at diffraction angles (2θ ± 0.2°) of 9.65° and 18.37°" means "having diffraction peaks at diffraction angles (2θ) of 9.45° to 9.85° and 18.17° to 18.57°", the phrase "having diffraction peaks at diffraction angles (2θ ± 0.2°) of 5.72° and 13.84°" means "having diffraction peaks at diffraction angles (2θ) of 5.52° to 5.92° and 13.64° to 14.04°", the phrase "having diffraction peaks at diffraction angles (2θ ± 0.2°) of 14.20° and 17.59°" means "having diffraction peaks at diffraction angles (2θ) of 14.00° to

14.40° and 17.39° to 17.79°", the phrase "having diffraction peaks at diffraction angles (2θ ± 0.2°) of 8.02° and 18.14°" means "having diffraction peaks at diffraction angles (2θ) of 7.82° to 8.22° and 17.94° to 18.34°", the phrase "having diffraction peaks at diffraction angles (2θ ± 0.2°) of 9.36° and 12.40°" means "having diffraction peaks at diffraction angles (2θ) of 9.16° to 9.56° and 12.20° to 12.60°", the phrase "having diffraction peaks at diffraction angles (2θ ± 0.2°) of 15.70° and 17.18°" means "having diffraction peaks at diffraction angles (2θ) of 15.50° to 15.90° and 16.98° to 17.38°", and the phrase "having diffraction peaks at diffraction angles (2θ ± 0.2°) of 6.48° and 9.58°" means "having diffraction peaks at diffraction angles (2θ) of 6.28° to 6.68° and 9.38° to 9.78°".

[0015] In the present specification, the phrase "having a peak at a chemical shift of about 162.4 ppm" means "having a peak substantially equivalent to 162.4 ppm when a ^{13}C Solid State Nuclear Magnetic Resonance spectrum (hereinafter abbreviated as 'a ^{13}C Solid State NMR spectrum') is measured under normal conditions", the phrase "having a peak at a chemical shift of about 128.0 ppm" means "having a peak substantially equivalent to 128.0 ppm when a ^{13}C Solid State NMR spectrum is measured under normal conditions", the phrase "having a peak at a chemical shift of about 102.3 ppm" means "having a peak substantially equivalent to 102.3 ppm when a ^{13}C Solid State NMR spectrum is measured under normal conditions", and the phrase "having a peak at a chemical shift of about 9.9 ppm" means "having a peak substantially equivalent to 9.9 ppm when a ^{13}C Solid State NMR spectrum is measured under normal conditions".

[0016] In the present specification, the phrase "having a peak at a chemical shift of about 160.2 ppm" means "having a peak substantially equivalent to 160.2 ppm when a ^{13}C Solid State NMR spectrum is measured under normal conditions", the phrase "having a peak at a chemical shift of about 126.6 ppm" means "having a peak substantially equivalent to 126.6 ppm when a ^{13}C Solid State NMR spectrum is measured under normal conditions", the phrase "having a peak at a chemical shift of about 105.6 ppm" means "having a peak substantially equivalent to 105.6 ppm when a ^{13}C Solid State NMR spectrum is measured under normal conditions", and the phrase

"having a peak at a chemical shift of about 7.8 ppm" means "having a peak substantially equivalent to 7.8 ppm when a ^{13}C Solid State NMR spectrum is measured under normal conditions".

[0017] In the present specification, the phrase "having an absorption band at a wavenumber of 1161 ± 1 cm^{-1}" means "having an absorption band at a wavenumber of 1160 cm^{-1} to 1162 cm^{-1}", the phrase "having an absorption band at a wavenumber of 1044 ± 1 cm^{-1}" means "having an absorption band at a wavenumber of 1043 cm^{-1} to 1045 cm^{-1}".

[0018] In the present specification, the phrase "having an absorption band at a wavenumber of 1068 ± 1 cm^{-1}" means "having an absorption band at a wavenumber of 1067 cm^{-1} to 1069 cm^{-1}", the phrase "having an absorption band at a wavenumber of 918 ± 1 cm^{-1}" means "having an absorption band at a wavenumber of 917 cm^{-1} to 919 cm^{-1}".

[0019] In the present specification, the phrase "having an absorption band at a wavenumber of 1324 ± 1 cm^{-1}" means "having an absorption band at a wavenumber of 1323 cm^{-1} to 1325 cm^{-1}", the phrase "having an absorption band at a wavenumber of 579 ± 1 cm^{-1}" means "having an absorption band at a wavenumber of 578 cm^{-1} to 580 cm^{-1}".

[0020] In the present specification, the phrase "having an absorption band at a wavenumber of 1750 ± 1 cm^{-1}" means "having an absorption band at a wavenumber of 1749 cm^{-1} to 1751 cm^{-1}", the phrase "having an absorption band at a wavenumber of 1224 ± 1 cm^{-1}" means "having an absorption band at a wavenumber of 1223 cm^{-1} to 1225 cm^{-1}".

[0021] In the present specification, the phrase "having an absorption band at a wavenumber of 1320 ± 1 cm^{-1}" means "having an absorption band at a wavenumber of 1319 cm^{-1} to 1321 cm^{-1}", the phrase "having an absorption band at a wavenumber of 997 ± 1 cm^{-1}" means "having an absorption band at a wavenumber of 996 cm^{-1} to 998 cm^{-1}".

[0022] In the present specification, the phrase "having an absorption band at a wavenumber of 1281 ± 1 cm^{-1}" means "having an absorption band at a wavenumber of 1280 cm^{-1} to 1282 cm^{-1}", the phrase "having an absorption band at a wavenumber of 985 ± 1 cm^{-1}" means "having an absorption band at a wavenumber of 984 cm^{-1} to 986 cm^{-1}".

[0023] [General Process for Preparation]

A process for preparing a crystalline form of the salts of carboxamide or the solvate of the salts according to the present invention is described in detail hereunder.

[0024] 1. Process for preparing a crystalline form of the hydrochloride or hydrobromide

A crystalline form of the hydrochloride or hydrobromide can be prepared by mixing the carboxamide and a solvent to dissolve, and followed by adding thereto hydrochloric acid or hydrobromic acid.

More specifically, for example, after mixing the carboxamide and a solvent and heating the mixture to dissolve the carboxamide, hydrochloric acid or hydrobromic acid is added thereto and the mixture is then cooled slowly to room temperature to give a crystalline form of the hydrochloride or hydrobromide.

As a solvent, an alcohol such as methanol, ethanol, 1-propanol or 2-propanol can be used, and preferably ethanol is used. Where necessary, the alcohol may be used after adding water thereto.

Although the amount of solvent is not particularly limited, preferably the amount used is 10- to 30-fold relative to the substrate amount, and more preferably 20-fold.

The amount of hydrochloric acid or hydrobromic acid used can be 1.0 to 1.5 equivalents relative to the substrate amount, and an equivalent of 1.1 is preferable.

While a heating temperature is not particularly limited, preferably the heating temperature is between 60 °C and reflux temperature, and more preferably reflux temperature.

Slow cooling from the heating temperature to room temperature can be performed in a period between 10 min and 24 hours.

[0025] 2. Process for preparing a crystalline form of the p-toluenesulfonate or sulfate

A crystalline form of the sulfate or p-toluenesulfonate can be prepared by mixing the carboxamide, a solvent and sulfuric acid or p-toluenesulfonic acid to dissolve the carboxamide.

More specifically, for example, a crystalline form of the p-toluenesulfonate or sulfate can be prepared by mixing the carboxamide, a solvent and p-toluenesulfonic acid or sulfuric acid, heating the mixture to dissolve the carboxamide, and then slowly cooling the mixture to room temperature.

As a solvent, for example, dimethyl sulfoxide, *N,N*-dimethylformamide, *N,N*-dimethylacetamide can be used, and dimethyl sulfoxide is preferable.

Although the amount of solvent is not particularly limited, preferably the amount used is 10- to 30-fold relative to the substrate amount, and more preferably 20-fold.

The amount of p-toluenesulfonic acid or sulfuric acid used can be 1.0 to 1.5 equivalents relative to the substrate amount, and an equivalent of 1.2 is preferable.

While a heating temperature is not particularly limited, the heating temperature is preferably between 60 °C and reflux temperature, more preferably between 70 and 100 °C, and further preferably 80 °C.

Slow cooling from the heating temperature to room temperature can be performed in a period between 10 min and 24 hours.

[0026] <u>3. Process for preparing a crystalline form of the methanesulfonate (Form A)</u>

(Preparation method 1)

A crystalline form of the methanesulfonate (Form A) can be prepared by mixing the carboxamide, a solvent and methanesulfonic acid to dissolve the carboxamide.

More specifically, a crystalline form of the methanesulfonate (Form A) can be prepared, for example, by mixing the carboxamide, a solvent and methanesulfonic acid, and heating the mixture to dissolve the carboxamide, and then slowly cooling the mixture to room temperature.

As a solvent, for example, methanol, ethanol, 2-propanol can be used, and methanol is preferable.

Although the amount of solvent is not particularly limited, preferably the amount used is 10- to 30-fold relative to the substrate

amount, and more preferably 20-fold.

The amount of methanesulfonic acid used can be 1.0 to 1.5 equivalents relative to the substrate amount, and an equivalent of 1.2 is preferable.

While a heating temperature is not particularly limited, the heating temperature is preferably between 60 °C and reflux temperature, and more preferably between 70 and 80 °C.

Slow cooling from a heating temperature to room temperature can be performed in a period between 1 and 24 hours, and preferably in a period between 3 and 12 hours.

(Preparation method 2)

A crystalline form of the methanesulfonate (Form A) can be prepared by mixing the carboxamide, acetic acid and methanesulfonic acid to dissolve the carboxamide.

More specifically, a crystalline form of the methanesulfonate (Form A) can be prepared, for example, by mixing the carboxamide, acetic acid and methanesulfonic acid, heating the mixture to dissolve the carboxamide, adding a poor solvent and slowly cooling the mixture to room temperature. Preferably, seed crystals of a crystalline form of the methanesulfonate (Form A) are added when the poor solvent is added.

Although the amount of acetic acid is not particularly limited, preferably the amount used is 5- to 20-fold relative to the substrate amount, and more preferably 10-fold.

The amount of methanesulfonic acid used can be 1.0 to 2.5 equivalents relative to the substrate amount, and an equivalent of 1.4 to 2.2 is preferable.

As a poor solvent, for example, methanol and ethanol can be used, and ethanol is preferred.

Although the amount of poor solvent is not particularly limited, preferably the amount used is 10- to 30-fold relative to substrate amount, and more preferably 20-fold. Further, the poor solvent can be added at one time or can be added dividedly 2 to 4 times, and preferably the poor solvent is divided and added 2 times. In this case, the ratio for the amount

of solvent added the first time and the amount of solvent added the second time is from 1:1 to 3:1, and preferably 3:2.

Although a heating temperature is not particularly limited, preferably the temperature is between 50 °C and reflux temperature, and more preferably 50 °C.

Slow cooling from a heating temperature to room temperature can be performed in a period between 10 min and 6 hours, and preferably in a period between 1 and 2 hours.

[0027] 4. Process for preparing a crystalline form of the methanesulfonate (Form B)

A crystalline form of the methanesulfonate (Form B) can be prepared by drying a crystalline form of the acetic acid solvate of the methanesulfonate (Form I) by a method such as drying under aeration to remove acetic acid.

[0028] 5. Process for preparing a crystalline form of the methanesulfonate (Form C)

(Preparation method 1)

A crystalline form of the methanesulfonate (Form C) can be prepared by heating a crystalline form of the dimethyl sulfoxide solvate of the methanesulfonate and slowly cooling to room temperature.

This preparation method can be carried out in the presence or absence of a solvent.

When using a solvent, examples of a solvent that can be used include ethyl acetate, isopropyl acetate and n-butyl acetate, and n-butyl acetate is preferable.

Although a heating temperature is not particularly limited, preferably the temperature is between 70 °C and reflux temperature, and more preferably reflux temperature.

(Preparation method 2)

A crystalline form of the methanesulfonate (Form C) can be prepared by mixing a crystalline form of the acetic acid solvate of the methanesulfonate (Form I) and a solvent, and stirring the mixture.

As a solvent, for example, an alcohol such as methanol, ethanol, or

2-propanol can be used, and ethanol is preferable.

Although a stirring temperature is not particularly limited, preferably the temperature is between 20 and 60 °C, and more preferably 40 °C.

(Preparation method 3)

A crystalline form of the methanesulfonate (Form C) can be prepared by mixing the carboxamide, acetic acid and methanesulfonic acid to dissolve the carboxamide.

More specifically, a crystalline form of the methanesulfonate (Form C) can be prepared, for example, by mixing the carboxamide, acetic acid and methanesulfonic acid, heating the mixture to dissolve the carboxamide, and then adding 2-propanol as a poor solvent and slowly cooling the solution to around 15 °C. Preferably, seed crystals of a crystalline form of the methanesulfonate (Form C) are added when the poor solvent is added, and isopropyl acetate is further added to accelerate precipitation.

Although the amount of acetic acid is not particularly limited, preferably the amount used is 5- to 10-fold relative to the substrate amount, and more preferably 7- to 8-fold.

The amount of methanesulfonic acid used can be an equivalent of 1.0 to 1.5 relative to the substrate amount, and an equivalent of 1.2 is preferable.

Although the amount of poor solvent is not particularly limited, preferably the amount used is 2- to 10-fold relative to the substrate amount, and more preferably 4- to 5-fold.

When adding isopropyl acetate, although the amount thereof is not particularly limited, a preferable amount is 2- to 10-fold relative to the substrate amount, and more preferably 5-fold.

Although a heating temperature is not particularly limited, a preferable temperature is 40 °C.

Slow cooling from a heating temperature to around 15 °C can be performed in a period between 10 min and 6 hours, and preferably in a period between 1 and 2 hours.

(Preparation method 4)

A crystalline form of the methanesulfonate (Form C) can be prepared by mixing the carboxamide, acetic acid and methanesulfonic acid to dissolve the carboxamide.

More specifically, a crystalline form of the methanesulfonate (Form C) can be prepared, for example, by mixing the carboxamide, acetic acid and methanesulfonic acid, dissolving the carboxamide at room temperature (or around 30 °C), adding 2-propanol as a poor solvent, slowly cooling the mixture to around 15 °C, filtering off precipitated crystals, and mixing and stirring the crystals and a solvent. Preferably, seed crystals of a crystalline form of the methanesulfonate (Form C) are added when the poor solvent is added.

Although the amount of acetic acid is not particularly limited, preferably the amount used is 5- to 20-fold relative to the substrate amount, and more preferably 10-fold.

The amount of methanesulfonic acid used can be an equivalent of 1.0 to 2.5 relative to the substrate amount, and an equivalent of 1.8 to 2.2 is preferable.

Although the amount of poor solvent is not particularly limited, preferably the amount used is 10- to 30-fold relative to the substrate amount, and more preferably 20-fold.

Slow cooling from room temperature (or around 30 °C) to around 15 °C can be performed in a period between 10 min and 4 hours, and preferably in a period between 30 min and 2 hours.

As a solvent to be mixed with the crystals which are filtered off, for example, an alcohol such as methanol, ethanol or 2-propanol can be used, and ethanol is preferred.

(Preparation method 5)

A crystalline form of the methanesulfonate (Form C) can be prepared by humidifying a crystalline form of the methanesulfonate (Form B).

[0029] <u>6. Process for preparing a crystalline form the dimethyl sulfoxide solvate of the methanesulfonate</u>

A crystalline form of the dimethyl sulfoxide solvate of the

methanesulfonate can be prepared by mixing the carboxamide, dimethyl sulfoxide and methanesulfonic acid, heating the mixture to dissolve the carboxamide, adding a poor solvent, and slowly cooling the mixture to around 15 °C. Preferably, seed crystals of a crystalline form of the methanesulfonate (Form A) are added when the poor solvent is added.

Although the amount of the dimethyl sulfoxide is not particularly limited, preferably the amount used is 5- to 20-fold relative to the substrate amount, and more preferably 8- to 10-fold.

The amount of methanesulfonic acid used can be an equivalent of 1.0 to 4.0 relative to the substrate amount, and an equivalent of 1.2 to 3.5 is preferable.

As a poor solvent, for example, ethyl acetate, isopropyl acetate, 1-propanol, 2-propanol can be used, and preferably ethyl acetate or 2-propanol is used.

Although the amount of poor solvent is not particularly limited, preferably the amount used is 10- to 30-fold relative to the substrate amount, and more preferably 20-fold. Further, the poor solvent can be added at one time or can be added dividedly 2 to 4 times, and preferably the poor solvent is divided and added 2 times. In this case, the ratio for the amount of solvent added the first time and the amount of solvent added the second time is from 1:1 to 1:5, and preferably 1:4.

Although a heating temperature is not particularly limited, preferably the temperature is between 50 and 100 °C, and more preferably between 60 and 80 °C.

Slow cooling from a heating temperature to around 15 °C can be performed in a period between 10 min and 6 hours, and preferably in a period between 1 and 2 hours.

[0030] <u>7. Process for preparing a crystalline of the hydrate of the methanesulfonate (Form F)</u>

A crystalline form of the hydrate of the methanesulfonate (Form F) can be prepared by mixing the carboxamide, acetic acid and methanesulfonic acid and to dissolve the carboxamide.

More specifically, a crystalline form of the hydrate of the

methanesulfonate (Form F) can be prepared, for example, by mixing the carboxamide, acetic acid and methanesulfonic acid, heating the mixture to dissolve the carboxamide, adding a poor solvent, and then slowly cooling the mixture to room temperature. Preferably, seed crystals of a crystalline of the methanesulfonate (Form A) are added when the poor solvent is added.

Although the amount of acetic acid is not particularly limited, preferably the amount used is 5- to 20-fold relative to the substrate amount, and more preferably 10-fold.

The amount of methanesulfonic acid used can be an equivalent of 1.0 to 2.0 relative to the substrate amount, and an equivalent of 1.3 to 1.6 is preferable.

As a poor solvent, for example, ethyl acetate, isopropyl acetate can be used, and ethyl acetate is preferable.

Although the amount of poor solvent is not particularly limited, preferably the amount used is 10- to 30-fold relative to the substrate amount, and more preferably 20-fold. Further, the poor solvent can be added at one time or can be added dividedly 2 to 4 times, and preferably the poor solvent is divided and added 2 times. In this case, the ratio for the amount of solvent added the first time and the amount of solvent added the second time is from 1:1 to 1:5, and a ratio of 1:3 is preferable.

Although a heating temperature is not particularly limited, preferably the temperature is between 40 and 60 °C, and more preferably 50 °C.

Slow cooling from a heating temperature to room temperature can be performed in a period between 10 min and 6 hours, and preferably in a period between 2 and 4 hours.

[0031] <u>8. Process for preparing a crystalline form of the acetic acid solvate of the methanesulfonate (Form I)</u>

A crystalline form of the acetic acid solvate of the methanesulfonate (Form I) can be prepared by mixing the carboxamide, acetic acid and methanesulfonic acid to dissolve the carboxamide.

More specifically, a crystalline form of the acetic acid solvate of the methanesulfonate (Form I) can be prepared, for example, by mixing the

carboxamide, acetic acid and methanesulfonic acid, heating the mixture to dissolve the carboxamide, adding a poor solvent, and slowly cooling the mixture to room temperature. Preferably, seed crystals of a crystalline form of the methanesulfonate (Form C) are added when the poor solvent is added, and isopropyl acetate is further added to accelerate precipitation.

Although the amount of acetic acid is not particularly limited, preferably the amount used is 5- to 10-fold relative to the substrate amount, and more preferably 7- to 8-fold.

The amount of methanesulfonic acid used can be an equivalent of 1.0 to 1.5 relative to the substrate amount, and an equivalent of 1.2 is preferable.

As a poor solvent, for example, 1-propanol, 1-butanol, tert-butanol can be used, and 1-propanol is preferred.

Although the amount of poor solvent is not particularly limited, a preferable amount is 5- to 20-fold relative to the substrate amount, and more preferably 8- to 10-fold. Further, the poor solvent can be added at one time or can be added dividedly 2 to 4 times, and preferably the poor solvent is divided and added 2 times. In this case, the ratio for the amount of solvent added the first time and the amount of solvent added the second time is from 1:1 to 1:5, and a ratio of 1:3.5 is preferable.

When adding isopropyl acetate, although the amount thereof is not particularly limited, a preferable amount is 2- to 10-fold relative to the substrate amount, and more preferably 5-fold.

Although a heating temperature is not particularly limited, a preferable temperature is 40 °C.

Slow cooling from a heating temperature to room temperature can be performed in a period between 10 min and 6 hours, and preferably in a period between 1 and 2 hours.

[0032] <u>9. Process for preparing a crystalline form of the ethanesulfonate (Form α)</u>

A crystalline form of the ethanesulfonate (Form α) can be prepared by mixing the carboxamide, a solvent and ethanesulfonic acid to dissolve the carboxamide.

More specifically, a crystalline form of the ethanesulfonate (Form α) can be prepared, for example, by mixing the carboxamide, a solvent and ethanesulfonic acid, heating the mixture to dissolve the carboxamide, adding a poor solvent, and then cooling this solution to room temperature.

As a solvent, for example, dimethyl sulfoxide can be used.

Although the amount of solvent is not particularly limited, a preferable amount is 5- to 20-fold relative to the substrate amount, and more preferably 10-fold.

The amount of ethanesulfonic acid used can be an equivalent of 1.0 to 1.5 relative to the substrate amount, and an equivalent of 1.2 is preferable.

As a poor solvent, for example, ethyl acetate can be used.

Although the amount of poor solvent is not particularly limited, preferably the amount used is 5- to 20-fold relative to the substrate amount, and more preferably 10-fold.

Although a heating temperature is not particularly limited, a preferable temperature is between 50 and 70 °C, and more preferably is 60 °C.

Cooling from a heating temperature to room temperature can be performed in a period between 5 min and 2 hours, and preferably in a period between 5 min and 1.5 hours.

[0033] <u>10. Process for preparing a crystalline form of the ethanesulfonate (Form β)</u>

(Preparation method 1)

A crystalline form of the ethanesulfonate (Form β) can be prepared by adding a solvent and water to a crystalline form of the ethanesulfonate (Form α) and stirring the mixture at room temperature.

As a solvent, for example, methanol, ethanol, and 2-propanol can be used, and ethanol is preferable.

Although the amount of solvent is not particularly limited, preferably the amount used is 5- to 20-fold relative to the substrate amount, and more preferably 10-fold.

Although the amount of water is not particularly limited, a

preferable amount is 1/10 to 1/2 of the ethanol amount, and more preferably 1/6 of the ethanol amount.

(Preparation method 2)

A crystalline form of the ethanesulfonate (Form β) can be prepared by mixing the carboxamide, acetic acid and ethanesulfonic acid to dissolve the carboxamide.

More specifically, a crystalline form of the ethanesulfonate (Form β) can be prepared, for example, by mixing the carboxamide, acetic acid and ethanesulfonic acid, heating the mixture to dissolve the carboxamide, adding a poor solvent and water, and cooling this solution to 0 °C. Preferably, seed crystals of a crystalline form of the ethanesulfonate (Form β) are added when the poor solvent is added.

Although the amount of acetic acid is not particularly limited, preferably the amount used is 2.5- to 10-fold relative to the substrate amount, and more preferably 5-fold.

The amount of ethanesulfonic acid used can be an equivalent of 1.0 to 1.5 relative to the substrate amount, and an equivalent of 1.2 is preferable.

As a poor solvent, for example, ethanol, and 2-propanol can be used, and 2-propanol is preferable.

Although the amount of poor solvent is not particularly limited, preferably the amount used is 10- to 40-fold relative to the substrate amount, and more preferably 30-fold. Further, the poor solvent can be added at one time or can be added dividedly 2 to 4 times, and preferably the poor solvent is divided and added 2 times. In this case, the ratio for the amount of solvent added the first time and the amount of solvent added the second time is from 1:1 to 1:5, and a ratio from 1:1.5 to 1:2 is preferable.

Although the amount of water is not particularly limited, a preferable amount is 1/10 to 1/30 of the poor solvent amount, and more preferably is 1/20 of the poor solvent amount.

Although a heating temperature is not particularly limited, a preferable temperature is between 50 and 70 °C, and more preferably 60 °C.

Cooling from a heating temperature to 0 °C can be performed in a

period between 10 min and 6 hours, and preferably in a period between 2 and 4 hours.

[0034] <u>11. Process for preparing a crystalline form of the dimethyl sulfoxide solvate of the ethanesulfonate</u>

A crystalline form of the dimethyl sulfoxide solvate of the ethanesulfonate can be prepared by mixing the carboxamide, dimethyl sulfoxide and ethanesulfonic acid, heating the mixture to dissolve the carboxamide, adding a poor solvent, and cooling the mixture to 0 °C. Preferably, seed crystals of a crystalline form of the ethanesulfonate (Form β) are added when the poor solvent is added.

Although the amount of dimethyl sulfoxide is not particularly limited, preferably the amount used is 5- to 20-fold relative to the substrate amount, and more preferably 10-fold.

The amount of ethanesulfonic acid used can be an equivalent of 1.0 to 1.5 relative to the substrate amount, and an equivalent of 1.2 is preferable.

As a poor solvent, for example, ethyl acetate can be used.

Although the amount of poor solvent is not particularly limited, preferably the amount used is 5- to 20-fold relative to the substrate amount, and more preferably 10-fold. Further, the poor solvent can be added at one time or can be added dividedly 2 to 4 times, and preferably the poor solvent is divided and added 2 times. In this case, the ratio for the amount of solvent added the first time and the amount of solvent added the second time is from 1:1 to 3:1, and a ratio of 3:2 is preferable.

Although a heating temperature is not particularly limited, a preferable temperature is between 50 and 70 °C, and more preferably 60 °C.

Cooling from a heating temperature to 0 °C can be performed in a period between 10 min and 6 hours, and preferably in a period between 1 and 2 hours.

[0035] When the crystals of the present invention are to be used as a medicament, it will normally be mixed with suitable additives for use as a formulation. However, the foregoing description does not limit the use of the crystals of the present invention as medicament in the state of intact

products.

Such additives may include excipients, binders, lubricants, disintegrators, coloring agents, taste correctives, emulsifiers, surfactants, dissolving aids, suspending agents, isotonizing agents, buffering agents, antiseptics, antioxidants, stabilizers, absorption accelerators and the like which are commonly used in pharmaceuticals, and they may be added in appropriate combinations as desired.

As examples of such excipients there may be mentioned lactose, white soft sugar, glucose, corn starch, mannitol, sorbitol, starch, alpha starch, dextrin, crystalline cellulose, soft silicic anhydride, aluminum silicate, calcium silicate, magnesium aluminometasilicate, calcium hydrogenphosphate, and the like.

As examples of binders there may be mentioned polyvinyl alcohol, methylcellulose, ethylcellulose, gum Arabic, tragacanth, gelatin, shellac, hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylcellulose sodium, polyvinylpyrrolidone, macrogol, and the like.

As examples of lubricants there may be mentioned magnesium stearate, calcium stearate, sodium stearyl fumarate, talc, polyethylene glycol, colloidal silica, and the like.

As examples of disintegrators, there may be mentioned crystalline cellulose, agar, gelatin, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin, pectin, low-substituted hydroxypropylcellulose, carboxymethylcellulose, carboxymethylcellulose calcium, croscarmellose sodium, carboxymethyl starch, and carboxymethyl starch sodium, and the like.

As coloring agents there may be mentioned those approved for addition to pharmaceuticals, such as iron sesquioxide, yellow iron sesquioxide, carmine, caramel, β-carotene, titanium oxide, talc, riboflavin sodium phosphate, yellow aluminum lake and the like.

As taste correctives there may be mentioned cocoa powder, menthol, aromatic powders, mentha oil, borneol, powdered cinnamon bark, and the like.

As emulsifiers or surfactants there may be mentioned stearyl triethanolamine, sodium lauryl sulfate, lauryl aminopropionic acid, lecithin, glycerin monostearate, sucrose fatty acid esters, glycerin fatty acid esters, and the like.

As dissolving aids there may be mentioned polyethylene glycol, propylene glycol, benzyl benzoate, ethanol, cholesterol, triethanolamine, sodium carbonate, sodium citrate, polysorbate 80, nicotinamide, and the like.

As suspending agents there may be mentioned the surfactants referred to above, as well as hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like.

As isotonizing agents there may be mentioned glucose, sodium chloride, mannitol, sorbitol and the like.

As buffering agents there may be mentioned buffering solutions of phosphate, acetate, carbonate, citrate and the like.

As antiseptics there may be mentioned methylparaben, propylparaben, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, and the like.

As antioxidants there may be mentioned sulfite, ascorbic acid, α-tocopherol, and the like.

The formulation may be in the form of an oral preparation such as a tablet, powder, granule, capsule, syrup, lozenge or inhalant; an external preparation such as a suppository, ointment, eye salve, tape, eye drop, nasal drop, ear drop, pap or lotion; or an injection.

An oral preparation will be formulated using an appropriate combination of additives among those mentioned above. The surface thereof may also be coated if necessary.

An external preparation will be formulated using an appropriate combination of additives among those mentioned above, and particularly excipients, binders, taste correctives, emulsifiers, surfactants, dissolving aids, suspending agents, isotonizing agents, antiseptics, antioxidants, stabilizers and absorption accelerators.

An injection will be formulated using an appropriate combination of additives among those mentioned above, and particularly emulsifiers, surfactants, dissolving aids, suspending agents, isotonizing agents, buffering agents, antiseptics, antioxidants, stabilizers and absorption accelerators.

[0036] When the crystals of the invention is to be used as a medicament, the dosage thereof will differ depending on the symptoms and age of the patient as well as the form of administration, but it will ordinarily be 100 μg to 10 g per day, administered at once or divided over several times.

[0037] The crystals of the present invention are extremely useful as an angiogenesis inhibitor, and are also useful as a prophylactic or therapeutic agent for a disease for which angiogenesis inhibition is effective, an angiogenesis inhibitor, an anti-tumor agent, a therapeutic agent for angioma, a cancer metastasis inhibitor, a therapeutic agent for retinal neovascularization, a therapeutic agent for diabetic retinopathy, a therapeutic agent for an inflammatory disease, a therapeutic agent for an inflammatory disease selected from the group consisting of deformant arthritis, rheumatoid arthritis, psoriasis and delayed hypersensitivity reaction, and a therapeutic agent for atherosclerosis.

[0038] When using the crystals of the present invention as an anti-tumor agent, examples of the tumor include a pancreatic cancer, a gastric cancer, a colon cancer, a breast cancer, a prostrate cancer, a lung cancer, a renal cancer, a brain tumor, a blood cancer or an ovarian cancer, and in particular, a gastric cancer, a colon cancer, a prostrate cancer, a lung cancer or a renal cancer are preferable.

[0039] Further, the crystals of the present invention exhibit a strong inhibitory activity for c-Kit kinase, and are useful as an anti-cancer agent for a cancer which has undergone a malignant alteration due to activation of c-Kit kinase (for example, acute myelogenous leukemia, mast cell leukemia, a small cell lung cancer, GIST, a testicular tumor, an ovarian cancer, a breast cancer, a brain tumor, neuroblastoma or a colon cancer). The crystals of the present invention are also useful as a therapeutic agent for a disease such as mastocytosis, allergy or asthma that is considered to be

caused by c-Kit kinase.

[Examples]

[0040] Hereunder, examples are described to facilitate further understanding of the present invention, however, the following examples are not intended to limit the scope of the present invention.

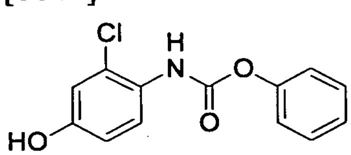
[0041] Preparation Example 1. Preparation of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (1)

Phenyl *N*-(4-(6-carbamoyl-7-methoxy-4-quinolyl)oxy-2-chlorophenyl)carbamate (17.5g; 37.7 mmol) disclosed in WO 02/32872 was dissolved in *N,N*-dimethylformamide (350 mL), and then cyclopropylamine (6.53 mL, 94.25 mmol) was added to the reaction mixture under a nitrogen atmosphere, followed by stirring overnight at room temperature. To the mixture was added water (1.75L), and the mixture was stirred. Precipitated crude crystals were filtered off, washed with water, and dried at 70 °C for 50 min. To the obtained crude crystals was added ethanol (300 mL), and then the mixture was heated under reflux for 30 min to dissolve, followed by stirring overnight to cool slowly down to room temperature. Precipitated crystals was filtered off and dried under vacuum, and then further dried at 70 °C for 8 hours to give the titled crystals (12.91 g; 80.2%).

[0042] Preparation Example 2. Preparation of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (2)

[0043] (1) Preparation of phenyl *N*-(2-chloro-4-hydroxyphenyl)carbamate

[0044]



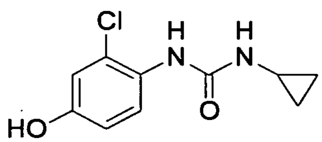
[0045] To a suspension of 4-amino-3-chlorophenol (23.7 g) in *N,N*-dimethylformamide (100 mL) was added pyridine (23.4 mL) while cooling in an ice bath, and phenyl chloroformate (23.2 mL) was added dropwise below 20 °C. After stirring at room temperature for 30 min, water

(400mL), ethyl acetate (300 mL), and 6N-HCl (48 mL) were added and stirred. The organic layer was separated off, washed twice with a 10% aqueous sodium chloride solution (200 mL), and dried over magnesium sulfate. The solvent was evaporated to give 46 g of the titled compound as a solid.

^{1}H-NMR Spectrum ($CDCl_3$) δ(ppm): 5.12 (1H, br s), 6.75 (1H, dd, J=9.2, 2.8 Hz), 6.92 (1H, d, J=2.8 Hz), 7.18-7.28 (4H, m), 7.37-7.43 (2H, m), 7.94 (1H, br s).

[0046] (2) Preparation of 1-(2-chloro-4-hydroxyphenyl)-3-cyclopropylurea

[0047]



[0048] To a solution of phenyl N-(2-chloro-4-hydroxyphenyl)carbamate in *N,N*-dimethylformamide (100 mL) was added cyclopropylamine (22.7 mL) while cooling in an ice bath, and the stirring was continued at room temperature overnight. Water (400 mL), ethyl acetate (300 mL), and 6N-HCl (55 mL) were added thereto, and the mixture was stirred. The organic layer was then separated off, washed twice with a 10% aqueous sodium chloride solution (200 mL), and dried over magnesium sulfate. The solvent was evaporated to give prism crystals, which were filtered off and washed with heptane to give 22.8 g of the titled compound (yield from 4-amino-3-chlorophenol: 77%).

^{1}H-NMR Spectrum ($CDCl_3$) δ(ppm): 0.72-0.77 (2H, m), 0.87-0.95 (2H, m), 2.60-2.65 (1H, m), 4.89 (1H, br s), 5.60 (1H, br s), 6.71 (1H, dd, J=8.8, 2.8 Hz), 6.88 (1H, d, J=2.8 Hz), 7.24-7.30 (1H, br s), 7.90 (1H, d, J=8.8 Hz)

[0049] (3) Preparation of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide

To dimethyl sulfoxide (20 mL) were added 7-methoxy-4-chloroquinoline-6-carboxamide (0.983 g), 1-(2-chloro-4-hydroxyphenyl)-3-cyclopropylurea (1.13 g) and cesium carbonate (2.71 g), and the mixture was heated and stirred at 70 °C for 23 hours. The reaction mixture was

cooled to room temperature, and water (50 mL) was added, and the resultant crystals were then filtered off to give 1.56 g of the titled compound (yield: 88%).

[0050] Preparation Example 3. Preparation of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (3)

7-Methoxy-4-chloroquinoline-6-carboxamide (5.00 kg, 21.13 mol), dimethyl sulfoxide (55.05 kg), 1-(2-chloro-4-hydroxyphenyl)-3-cyclopropylurea (5.75 kg, 25.35 mol) and potassium t-butoxide (2.85 kg, 25.35 mol) were introduced in this order into a reaction vessel under a nitrogen atmosphere. The mixture was stirred for 30 min at 20 °C, and the temperature was raised to 65 °C over 2.5 hours. The mixture was stirred at the same temperature for 19 hours. 33% (v/v) acetone-water (5.0 L) and water (10.0 L) were added dropwise over 3.5 hours. After the addition was completed, the mixture was stirred at 60 °C for 2 hours. 33% (v/v) acetone-water (20.0 L) and water (40.0 L) were added dropwise at 55 °C or more over 1 hour. After stirring at 40 °C for 16 hours, precipitated crystals were filtered off using a nitrogen pressure filter, and was washed with 33% (v/v) acetone-water (33.3 L), water (66.7 L), and acetone (50.0 L) in that order. The obtained crystals were dried at 60 °C for 22 hours using a conical vacuum dryer to give 7.78 kg of the titled compound (yield: 96.3%).

[0051] ^{1}H-NMR chemical shift values for 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamides obtained in Preparation Examples 1 to 3 corresponded to those for 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide disclosed in WO 02/32872.

[0052] Example 1. A crystalline form of the hydrochloride of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide

A suspension of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-

quinolinecarboxamide (854 mg, 2.0 mmol) in ethanol (17 mL) was stirred, and 2N hydrochloric acid (1.1 mL, 2.2 mmol) was added dropwise to the reaction mixture while refluxing using an oil bath with an external temperature of 100 °C. After confirming that the suspension had changed into a solution, the heating of the oil bath was stopped, and the mixture was cooled slowly to room temperature while immersed in the oil bath, followed by stirring overnight. Ethanol (8.6 mL) was added to the reaction mixture, and resultant crystals were filtered off, washed with ethanol (4.3 mL x 2), dried under aeration on filter paper (1.5 hours), and then dried (23 hours) with hot air at 70 °C to give the titled crystals (786.1 mg, 85%).

^{1}H-NMR Spectrum (DMSO-d_6) δ(ppm): 0.30-0.50 (2H, m), 0.60-0.70 (2H, m), 2.56 (1H, m), 4.06 (3H, s), 6.86 (1H, d, J=6.4Hz), 7.29-7.35 (2H, m), 7.60 (1H, d, J=2.8Hz), 7.64 (1H, s), 7.88 (1H, s), 7.95 (1H, s), 8.07 (1H, s), 8.34 (1H, d, J=9.2Hz), 8.70 (1H, s), 8.91 (1H, d, J=6.4Hz).

[0053] Example 2. A crystalline form of the hydrobromide of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide

A suspension of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (500 mg, 1.17 mmol) in ethanol (10 mL) was stirred, and an aqueous solution of 1N hydrobromic acid (1.3 mL, 1.3 mmol) was then added dropwise to the reaction mixture while refluxing using an oil bath with an external temperature of 100 °C. After water (2.0 mL) was gradually added to the mixture to form a solution, the heating of the oil bath was stopped, and the mixture was cooled slowly to room temperature while immersed in the oil bath, followed by stirring overnight. Precipitated crystals were filtered off, washed with ethanol (2.5 mL x 2), dried under aeration on filter paper (15 min), and then dried (22 hours) with hot air at 100 °C to give the titled crystals (483.7 mg, 81%).

^{1}H-NMR Spectrum (DMSO-d_6) δ(ppm): 0.40-0.50 (2H, m), 0.60-0.70 (2H, m), 2.58 (1H, m), 4.09 (3H, s), 6.89 (1H, d, J=6.4Hz), 7.26 (1H, d, J=2.8Hz), 7.33 (1H, dd, J=2.8, 9.2Hz), 7.59 (1H, s), 7.62 (1H, d, J=2.8Hz), 7.90 (1H, s), 7.96 (1H, s), 8.06 (1H, s), 8.36 (1H, d, J=9.2Hz), 8.72 (1H, s),

8.93 (1H, d, J=6.4Hz).

[0054] Example 3. A crystalline form of the p-toluenesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide

Dimethyl sulfoxide (1.5 mL) and p-toluenesulfonic acid monohydrate (80 mg, 0.422 mmol) were added to 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (150 mg, 0.351 mmol) at room temperature. Although a solution was temporarily formed, crystals precipitated immediately. Therefore, dimethyl sulfoxide (2.25 mL) was added to the reaction mixture at 80 °C to dissolve the crystals. The mixture was cooled slowly to room temperature, and stirred for 14 hours. Precipitated crystals were filtered off and dried at 60 °C to give the titled crystals (177 mg).

^{1}H-NMR Spectrum (400 MHz, DMSO-d_6) δ(ppm): 0.39 (2H, m), 0.63 (2H, m), 2.24 (3H, s), 2.54 (1H, m), 4.04 (3H, s), 6.88 (1H, d, J=6.4 Hz), 7.05 (1H, s), 7.07 (1H, s), 7.21 (1H, d, J=2.8 Hz), 7.31 (1H, dd, J=2.6, 9.3 Hz), 7.41 (1H, s), 7.43 (1H, s), 7.59 (1H, d, J=2.8 Hz), 7.86 (1H, s), 7.92 (1H, s), 8.02 (1H, s), 8.32 (1H, d, J=9.6 Hz), 8.68 (1H, s), 8.91 (1H, d, J=6.4 Hz)

[0055] Example 4. A crystalline form of the sulfate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide

Dimethyl sulfoxide (1.5 mL) and sulfuric acid (23 μL, 0.422 mmol) were added to 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (150 mg, 0.351 mmol) at room temperature. Although a solution was temporarily formed, crystals precipitated immediately. Therefore, dimethyl sulfoxide (2.25 mL) was added to the reaction mixture at 80 °C to dissolve the crystals. The mixture was cooled slowly to room temperature, and stirred for 16 hours. Precipitated crystals were filtered off and dried at 60 °C to give the titled crystals (174 mg).

^{1}H-NMR Spectrum (400 MHz, DMSO-d_6) δ(ppm): 0.39 (2H, m), 0.63 (2H, m), 2.46 (2H, d, J=1.2 Hz), 2.52 (1H, m), 4.04 (3H, s), 6.88 (1H,

d, J=5.8Hz), 7.21 (1H, s), 7.31 (1H, d, J=8.2Hz), 7.56 (1H, s), 7.59 (1H, s), 7.86 (1H, s), 7.93 (1H, s), 8.02 (1H, s), 8.33 (1H, d, J=8.2Hz), 8.68 (1H, s), 8.91 (1H, d, J=5.8Hz)

[0056] Example 5. A crystalline form of the methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form A)

(Preparation method 1)

In a mixed solution of methanol (14 mL) and methanesulfonic acid (143 μL, 1.97 mmol) was dissolved 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (700 mg, 1.64 mmol) at 70 °C. After confirming the dissolution of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide, the reaction mixture was cooled to room temperature over 5.5 hours, further stirred at room temperature for 18.5 hours, and crystals were filtered off. The resultant crystals were dried at 60 °C to give the titled crystals (647 mg).

(Preparation method 2)

In a mixed solution of acetic acid (6 mL) and methanesulfonic acid (200 μL, 3.08 mmol) was dissolved 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (600 mg, 1.41 mmol) at 50 °C. After confirming the dissolution of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide, ethanol (7.2 mL) and seed crystals of a crystalline form of the methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form A) (12 mg) were added in this order to the reaction mixture, and ethanol (4.8 mL) was further added dropwise over 2 hours. After the addition was completed, the reaction mixture was stirred at 40°C for 1 hour then at room temperature for 9 hours, and crystals were filtered off. The resultant crystals were dried at 60 °C to give the titled crystals (545 mg).

[0057] <u>Example 6. A crystalline form of the methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form B)</u>

A crystalline form of the acetic acid solvate of the methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form I) (250 mg) obtained in Example 10 was dried under aeration at 30 °C for 3 hours and at 40 °C for 16 hours to give the titled crystals (240 mg).

[0058] <u>Example 7. A crystalline form of the methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form C)</u>

(Preparation method 1)

n-Butyl acetate (12 mL) was added to a crystalline form of the dimethyl sulfoxide solvate of the methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (600 mg, 1.15 mmol) obtained in Example 8 (Preparation method 1), and the reaction mixture was stirred at 115 °C for 10 hours and further stirred at room temperature for 1.5 hours Resultant crystals were then filtered off and dried at 60 °C to give the titled crystals (503 mg).

(Preparation method 2)

Ethanol (6.4 mL) was added to a crystalline form of the acetic acid solvate of the methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form I) (1.28 g) obtained in Example 10 to dissolve at 40 °C, and then the reaction mixture was stirred at the same temperature for 36 hours. Precipitated crystals were filtered off and dried at 50 °C to give the titled crystals (0.87 g).

(Preparation method 3)

To a mixed solution of acetic acid (14 mL) and methanesulfonic acid (0.37 mL, 5.62 mmol) 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-

quinolinecarboxamide (2.00 g, 4.69 mmol) was added to dissolve at 40 °C. After confirming the dissolution, 2-propanol (9 mL) and seed crystals of a crystalline form of the methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form C) (100 mg) were added in this order to the reaction mixture, and the reaction mixture was stirred for 20 min. Isopropyl acetate (10 mL) was then further added dropwise over 30 min. After the addition of the isopropyl acetate was completed, the reaction mixture was stirred for 1.5 hours, and further stirred at 15 °C for 14 hours. Precipitated crystals were filtered off and dried at 60 °C to give the titled crystals (2.22 g).

(Preparation method 4)

To a suspension of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (1.28 g, 3 mmol) in acetic acid (12.8 ml) was added methanesulfonic acid (0.408 ml, 6.3 mmol), and the mixture was stirred at room temperature to dissolve. The reaction mixture was heated with a bath at a temperature of 30 °C, and 2-propanol (7.7 ml) was added. Seed crystals of a crystalline form of the methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form C) was added, and 2-propanol was further added 14 times by every amount of 1.28 ml over 44 min. The warm bath was removed, the reaction mixture was stirred for 10 min at room temperature, then for 5 min in a water bath, and for 25 min in a water bath with a small amount of ice (internal temperature: 17.6 °C). Resultant crystals were filtered off and washed with 2-propanol (10 ml). The filtered crystals were stirred in ethanol (6.4 ml) at room temperature for 1 hour. Resultant crystals were filtered off, washed with ethanol (4 ml) and dried at 60 °C to give the titled crystals (1068 mg).

[0059] <u>Example 8. A crystalline form of the dimethyl sulfoxide solvate of methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide</u>

(Preparation method 1)

Dimethyl sulfoxide (7 mL) was added at room temperature to 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (700 mg, 1.640 mmol) and the mixture was dissolved at 80 °C. Methanesulfonic acid (143 μL, 1.97 mmol), ethyl acetate (1.4 mL), and seed crystals of a crystalline form of the methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form A) were added in this order to the reaction mixture at 60 °C, and ethyl acetate (5.6 mL) was further added dropwise over 45 min. 15 min after completion of the addition of the ethyl acetate, the reaction mixture was cooled to room temperature over 1 hour, and stirred at the same temperature for 18 hours. Precipitated crystals were filtered off and dried at 60 °C to give the titled crystals (746 mg).

(Preparation method 2)

Dimethyl sulfoxide (6.8 mL) was added at room temperature to 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (854 mg, 2 mmol) and the mixture was dissolved at 60 °C. Methanesulfonic acid (389 μL, 6 mmol) and seed crystals of a crystalline form of the methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form A) were added in this order to the reaction mixture at the same temperature, and 2-propanol (6.8 mL) was then added dropwise over 30 min. After completion of the addition of the 2-propanol, the reaction mixture was cooled to 15 °C over 2 hours, and then stirred at the same temperature for 30 min. Precipitated crystals were filtered off and dried at 60 °C to give the titled crystals (1095 mg).

(Preparation method 3)

Dimethyl sulfoxide (6.8 mL) was added at room temperature to 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (854 mg, 2 mmol) and the mixture was dissolved at 62 °C. Methanesulfonic acid (454 μL, 7 mmol) and seed crystals of a crystalline form of the methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-

quinolinecarboxamide (Form A) were added in this order to the reaction mixture at the same temperature, and 2-propanol (13.6 mL) was then added dropwise over 1 hour. After the completion of the addition of the 2-propanol, the reaction mixture was cooled to 15 °C over 2 hours, and then stirred at the same temperature for 30 min. Precipitated crystals were filtered off and dried at 60 °C to obtain the titled crystal (1082 mg).

[0060] Example 9. A crystalline form of the hydrate of the methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form F)

In a mixed solution of acetic acid (1.5 mL) and methanesulfonic acid (31 μL, 0.422 mmol) was dissolved 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (150 mg, 0.351 mmol) at 50 °C. After confirming the dissolution, ethyl acetate (0.6 mL) and a crystalline form of the methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form A) obtained in Example 5 (Preparation method 1) were added In this order to the reaction mixture, and ethyl acetate (1.8 mL) was further added dropwise over 2 hours. After the addition of ethyl acetate was completed, the reaction mixture was stirred at 50 °C for 30 min, and then stirred at room temperature for 7.5 hours. Precipitated crystals were filtered off and dried at 60 °C to give the titled crystals (176 mg).

[0061] Example 10. A crystalline form of the acetic acid solvate of the methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form I)

In a mixed solution of acetic acid (14 mL) and methanesulfonic acid (0.36 mL, 5.62 mmol) was dissolved 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (2.00 g, 4.69 mmol) at 40 °C. After confirming the dissolution, 1-propanol (4 mL) and seed crystals of a crystalline form of the

methanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form C) (100 mg) were added in this order to the reaction mixture, and 1-propanol (14 mL) and isopropyl acetate (10 mL) were further added dropwise over 1 hour. After the addition was completed, the reaction mixture was stirred at 40 °C for 1 hour, and then stirred at 25 °C for a further 40 min. Precipitated crystals were filtered off to give the titled crystals (2.61 g).

[0062] The ^{1}H-NMR chemical shift values for the methanesulfonate are as follows:

^{1}H-NMR Spectrum (DMSO-d_6) δ(ppm): 0.44 (2H, m), 0.67 (2H, m), 2.36 (3H, s), 2.59 (1H, m), 4.09 (3H, s), 6.95 (1H, d, *J*=7 Hz), 7.25 (1H, d, *J*=2 Hz), 7.36 (1H, dd, *J*=3, 9 Hz), 7.63 (1H, d, *J*=3 Hz), 7.65 (1H, s), 7.88 (1H, brs), 7.95 (1H, brs), 8.06 (1H, s), 8.37 (1H, d, *J*=9 Hz), 8.73 (1H, s), 8.97 (1H, d, J= 7 Hz)

[0063] <u>Example 11. A crystalline form of the ethanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form α)</u>

(Preparation method 1)

Dimethyl sulfoxide (1.5 mL) and ethanesulfonic acid (34 μL, 0.422 mmol) were added to 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (150 mg, 0.351 mmol) and the mixture was dissolved at room temperature. Ethyl acetate (1.5 mL) was added dropwise to the reaction mixture at 60 °C over 1.5 hours. 30 min after the addition of ethyl acetate was completed, the reaction mixture was cooled to room temperature over 1.5 hours, and then stirred at room temperature for a further 7 hours. Precipitated crystals were filtered off and dried at 60 °C to give the titled crystals (176 mg).

(Preparation method 2)

Ethanol (40 mL) and ethanesulfonic acid (459 μL, 5.622 mmol) were added to 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (150 mg, 0.351 mmol) at room

temperature and the mixture was dissolved at 65 °C. The reaction mixture was cooled with a bath at a temperature of 22 °C, and seed crystals of a crystalline form of the ethanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form α) was added. The mixture was stirred for further 7 hours. Precipitated crystals were filtered off and dried at 70 °C to give the titled crystals (1.55g).

[0064] Example 12. A crystalline form of the ethanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form β)

(Preparation method 1)

Ethanol (3 mL) and water (0.5 mL) were added to a crystalline form of the ethanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form α) (198 mg) obtained in Example 11, and the reaction mixture was stirred at room temperature for 3 hours. Crystals were filtered off and dried at 60 °C to give the titled crystals (89 mg).

(Preparation method 2)

Acetic acid (0.75 mL) and ethanesulfonic acid (34 μL, 0.422 mmol) were added at room temperature to 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (150 mg, 0.351 mmol), and the mixture was then dissolved at 60 °C. To the reaction mixture were added water (0.225 mL), 2-propanol (2 mL), a crystalline form of the ethanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form β) obtained in (Preparation method 1) of Example 12, and 2-propanol (2.5 mL) in this order, and the mixture was then cooled to 0 °C over 2.5 hours, and stirred for 30 min. Precipitated crystals were filtered off and dried at 60 °C to give the titled crystals (139 mg).

[0065] Example 13. A crystalline form of the dimethyl sulfoxide solvate of the ethanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-

quinolinecarboxamide

Dimethyl sulfoxide (4 mL) was added at room temperature to 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (400 mg, 0.937 mmol), and the mixture was then dissolved at 60 °C. To the reaction mixture were added ethanesulfonic acid (92 μL, 1.124 mmol), ethyl acetate (2.4 mL) and a crystalline form of the ethanesulfonate of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide (Form β) obtained in (Preparation method 1) of Example 12 in this order, and the mixture was then stirred at 60 °C for 20 min. After a further addition of ethyl acetate (1.6 mL), the reaction mixture was once heated to 80 °C, and then cooled to 0 °C over 1.5 hours. Precipitated crystals were filtered off and dried at 60 °C to give the titled crystals (523 mg).

[0066] The ^{1}H-NMR chemical shift values for the ethanesulfonate are as follows:

^{1}H-NMR Spectrum (DMSO-d_6) δ(ppm): 0.43 (2H, m), 0.66 (2H, m), 1.05 (3H, t, J=7.4 Hz), 2.38 (2H, q, J=7.4 Hz), 2.58 (1H, m), 4.08 (3H, s), 6.88 (1H, s), 7.24 (1H, s), 7.34 (1H, d, J=9.0 Hz), 7.60 (1H, s), 7.61 (1H, s), 7.88 (1H, s), 7.94 (1H, s), 8.05 (1H, s), 8.36 (1H, d, J=9.0 Hz), 8.72 (1H, s), 8.92 (1H, s)

[0067] Test Example 1. Test for measuring dissolution rate

[Method]

The dissolution rates of the following crystals were measured under the conditions described below by the rotating disk method (see, J. H. Woods et al., J. Pharm. Soc., 54, 1068 (1955)): a crystalline form of the free carboxamide (obtained in Preparation Example 1), a crystalline form of the hydrochloride of the carboxamide (obtained in Example 1), a crystalline form of the hydrobromide of the carboxamide (obtained in Example 2), a crystalline form of the methanesulfonate (hereunder, referred to as "mesylate") of the carboxamide (Form A) (obtained in Example 5), a crystalline form of the mesylate of the carboxamide (Form C) (obtained in Example 7) and a crystalline form of the ethanesulfonate (hereunder,

referred to as "esylate") (Form β) (obtained in Example 12). The dissolution rates were calculated based on a range in which linearity was maintained in the relation between concentration and time at the initial stage of dissolution.

(Rotating disk method conditions)

Solvent: "2nd fluid" (pH 6.8, 500 mL) as described in Japanese Pharmacopoeia 14th Edition, General Tests (disintegration test)

Temperature: 37 °C

Disk rotation speed: 50 rpm

Area of powder contacting with solvent on disk: 1 cm^2

Sampling amount: approx. 1 mL

(HPLC conditions)

Column: Cadenza CD-18 (Imtakt Corporation; inner diameter 4.6 mm, column length 100 mm, particle size 3 μm)

Column temperature: 40 °C

Flow rate: 1.0 mL/min

Mobile phase:

Solution A: $H_2O:CH_3CN:HClO_4$ = 990:10:1 (v/v/v)

Solution B: $CH_3CN:H_2O:HClO_4$ = 900:100:1 (v/v/v)

Concentration of solution B: 20%

Injection amount: 100 μL

Detection: ultraviolet absorbance photometer (wavelength: 252 nm)

Temperature of auto sampler: 25 °C

[Results]

Table 1 shows the dissolution rates.

[0068] [Table 1]

	dissolution rate (μg/min/cm^2)
free form	0.8
hydrochloride	4.7
hydrobromide	8.7
mesylate (Form A)	11.8
mesylate (Form C)	15.5
esylate (Form β)	18.5

[0069] For each crystal of the salts, the dissolution rate increased significantly in comparison to a crystalline form of the free form of the carboxamide. The increase of dissolution rate was particularly remarkable for a crystalline form of the mesylate and a crystalline form of the esylate.

[0070] Test Example 2. Study of pharmacokinetics in beagle dogs

[Method]

A crystalline form of the free form of the carboxamide (obtained in Preparation Example 1), a crystalline form of the hydrobromide of the carboxamide (obtained in Example 2) and a crystalline form of the mesylate of the carboxamide (Form A) (obtained in Example 5) were grounded in a mortar, encapsulated in a gelatin capsule, and then administered orally to beagle dogs (n = 3). After administration, 10 mL of water was further administered orally. The dose was set such that it was equivalent to 3 mg/kg as a free form, and the beagle dogs were fasted from the day before administration, and fed again 8 hours after the administration.

To calculate bioavailability (BA), a test was conducted using a single intravenous administration. More specifically, a crystalline form of the free from of the carboxamide was dissolved in a solution containing 10% dimethyl sulfoxide, 50% polyethylene glycol 400 and 40% 0.1M aqueous solution of hydrochloric acid and administered intravenously through cephalic vein of the foreleg.

The plasma concentration of the carboxamide was measured by HPLC-UV method after sampling blood from cephalic vein of the foreleg. Based on the concentration, pharmacokinetic parameters were calculated for each individual by the moment method. Further, based on the calculated parameters, the mean value and standard error thereof were calculated.

[Results]

Table 2 shows the pharmacokinetic parameters, and Fig. 1 shows the relation between time and plasma concentration.

[0071] [Table 2]

		free form	hydrobromide	mesylate (Form A)
time to reach maximum plasma concentration (T_{max})	(hr)	1.17 ± 0.4	2.67 ± 0.7	1.67 ± 0.3
Maximum plasma concentration (C_{max})	(ng/mL)	53.3 ± 9.9	480.4 ± 31.4	397.1 ± 100.1
plasma concentration after 24 hours (C_{24hr})	(ng/mL)	24.0 ± 9.0	100.5 ± 81.7	17.1 ± 2.5
$AUC_{0\text{-}24hr}$	(μg hr/mL)	0.6 ± 0.0	4.8 ± 0.2	3.0 ± 0.4
BA	(%)	9.1 ± 0.4	73.5 ± 2.3	46.2 ± 5.9

[0072] The maximum plasma concentration and BA increased significantly for each crystalline form of the salts in comparison to a crystalline form of the free form.

[0073] Test Example 3. Evaluation of hygroscopicity and solid stability

[Method]

The hygroscopicity and solid stability of a crystalline form of the mesylate of the carboxamide (Form A) (obtained in Example 5), a crystalline form of the mesylate of the carboxamide (Form C) (obtained in Example 7), a crystalline form of the acetic acid solvate of the mesylate of the carboxamide (Form I) (obtained in Example 10) and a crystalline form of the esylate of the carboxamide (Form β) (obtained in Example 12) were measured under the following conditions.

1. Storage conditions for the hygroscopicity test (period: 1 week)

a-1. 25 °C, relative humidity 75%

b-1. 25 °C, relative humidity 93%

2. Storage conditions for the solid stability test (period: 2 weeks)

a-2. -20 °C (well closed)

b-2. 25 °C, light irradiation (1000 lx; shading with aluminum foil, well closed)

c-2. 25 °C, light irradiation (1000 lx; well closed)

d-2. 40 °C, relative humidity 75%

e-2. 60 °C (well closed except the following case: slightly open in the case of a crystalline form of the acetic acid solvate of the mesylate (Form I))

3. Method for measuring the impurity amount by HPLC

After storage, the sample solution was prepared by adding a mixed solvent of water and methanol (3:1) to each crystal at 0.1 mg/mL as final concentration.

Tests were conducted by the HPLC method for these sample solutions under the measurement conditions described below, and the eluted peak areas were measured to determine the total impurity amount by the relative area method (impurities of 0.05% or more were counted).

(Formula for calculating total impurity amount)

Individual impurity amount (%) = (the peak area for the individual impurity) × 100/{(the peak area for carboxamide) + (sum of the peak areas for impurities)}

Total impurity amount (%) = sum of individual impurity amounts

(HPLC measurement conditions)

Column: Mightysil RP-18 GP (Kanto Kagaku; inner diameter 4.6 mm, column length 150 mm, particle size 3 μm)

Column temperature: constant temperature in vicinity of 40 °C

Flow rate: 1.0 mL/min

Mobile phase:

Solution A: H_2O:CH_3CN:$HClO_4$ = 990:10:1 (v/v/v)

Solution B: CH_3CN:H_2O:$HClO_4$ = 900:100:1 (v/v/v)

Gradient conditions

[0074] [Table 3]

time (min)	concentration of Solution B (%)
0	5
3	20
15	20
30	100
30.01	5
35	5

[0075]

Injection amount: 10 μL

Detection: ultraviolet absorbance photometer (wavelength: 252 nm)

Temperature of auto sampler: constant temperature in vicinity of 10 °C

4. Powder X-ray diffraction

Analysis was carried out according to "X-Ray Powder Diffraction Method" described in Japanese Pharmacopoeia 14th Edition, General Tests (B-614 to 619) under the following measurement conditions.

Apparatus: RINT-2000 (manufactured by Rigaku Denki KK)

X-ray: CuKα ray

Monochrometer: curved crystal monochrometer

Goniometer: vertical goniometer

Counter: scintillation counter

Applied voltage: 40 kV

Charging current: 200 mA

Scan speed: 5°/min

Scan axis: 2θ/θ

Scan range: 2θ = 5° to 40°

Divergent slit: 0.5°

Scattering slit: 0.5°

Receiving slit: 0.3 mm

5. Measurement of water content

Measurement was carried out according to the Water Determination as described in Japanese Pharmacopoeia 14th Edition, General Tests (B-318 to 331) using 6 to 10 mg of each crystal.

[Results]

The results of hygroscopicity evaluation are shown in Table 4 to Table 7.

[0076] [Table 4]

Evaluation of hygroscopicity of a crystalline form of the mesylate (Form A)

condition	water content (%)	crystal form
initial	0.3	A
a-1	0.5	A
b-1	0.7	A

[0077] [Table 5]

Evaluation of hygroscopicity of a crystalline form of the mesylate (Form C)

condition	water content (%)	crystal form
initial	0.7	C
a-1	0.6	C
b-1	0.7	C

[0078] [Table 6]

Evaluation of hygroscopicity of a crystalline form of the acetic acid solvate of the mesylate (Form I)

condition	water content (%)	crystal form
initial	2.9	I
a-1	0.6	C
b-1	0.8	C

[0079] [Table 7]

Evaluation of hygroscopicity of a crystalline form of the esylate (Form β)

condition	water content (%)	crystal form
initial	1.7	β
a-1	1.7	β
b-1	1.4	β

[0080] Water content did not change remarkably for a crystalline form of the mesylate (Form A), a crystalline form of the mesylate (Form C) and a crystalline form of the esylate (Form β), and hygroscopicity was not observed. Neither remarkable change in appearance nor crystal transition was observed.

In contrast, with regard to a crystalline form of the acetic acid solvate of the mesylate (Form I), a decrease in water content was observed as well as transition to a crystalline form of the mesylate (Form C).

The results of evaluation of solid stability are shown in Table 8 to Table 11.

[0081] [Table 8]

Evaluation of solid stability of a crystalline form of the mesylate (Form A)

condition	total impurity (%)	water content (%)	crystal form
initial	4.02	0.3	A
a-2	3.90	0.0	A
b-2	3.95	0.0	A
c-2	4.23	0.1	A
d-2	3.90	0.2	A
e-2	3.97	0.2	A

[0082] [Table 9]

Evaluation of solid stability of a crystalline form of the mesylate (Form C)

condition	total impurity (%)	water content (%)	crystal form
initial	2.11	0.7	C
a-2	2.10	0.7	C
b-2	2.09	0.8	C
c-2	2.22	0.7	C
d-2	2.06	0.6	C
e-2	2.18	0.5	C

[0083] [Table 10]

Evaluation of solid stability of a crystalline form of the acetic acid solvate of the mesylate (Form I)

condition	total impurity (%)	water content (%)	crystal form
initial	0.62	2.9	I
a-2	0.67	3.1	I
b-2	0.66	3.1	I
c-2	0.87	2.9	I
d-2	0.61	0.9	C
e-2	0.84	0.3	B

[0084] [Table 11]

Evaluation of solid stability of a crystalline form of the esylate (Form β)

condition	total impurity (%)	water content (%)	crystal form
initial	0.55	1.7	β
a-2	0.48	2.0	β
b-2	0.46	2.5	β
c-2	0.49	2.1	β
d-2	0.48	2.0	β
e-2	0.51	2.2	β

[0085] For a crystalline form of the mesylate (Form A), a crystalline form of the mesylate (Form C) and a crystalline form of the esylate (Form β), neither remarkable changes in water content and appearance nor crystal transition was observed.

In contrast, with regard to a crystalline form of the mesylate (Form I), neither crystal transition nor remarkable changes in total impurity amount, water content and appearance were observed when stored in a well closed container. However, for a sample stored under conditions of 40 °C and relative humidity of 75%, a decrease in water content was observed along with transition to a crystalline form of the mesylate (Form C). Further, for a sample stored at 60 °C in a slightly opened container, a decrease in water content was observed along with transition to a crystalline form of the mesylate (Form B).

[0086] <u>Test Example 4. Powder X-ray diffraction of a crystalline form of the mesylate (Form B) (obtained in Example 6) with a treatment of humidification</u>

[Method]

Powder X-ray diffraction was measured under the measurement conditions similar to those in 4. (powder X-ray diffraction) of Test Example 3. Humidification was carried out using a humidity control unit HUM-1A (manufactured by Rigaku Denki KK), to sequentially adjust relative humidity to 3%, 30%, 50%, 60%, 70%, 75%, 80% and 85% at room temperature.

[Results]

A crystalline form of the mesylate (Form B) remained its state and did not exhibit a crystal transition at a relative humidity from 3% to 70%. However it changed to a mixture of crystalline forms of the mesylate (Form B) and (Form C) at a relative humidity of 75% and 80%, a transition to a crystalline form of the mesylate (Form C) was observed. At a relative humidity of 85%, there was a complete transition to a crystalline form of the mesylate (Form C).

[0087] Test Example 5. Temperature-controlled powder X-ray diffraction of a crystalline form of the dimethyl sulfoxide solvate of the mesylate (obtained in Example 8 (preparation method 1))

[Method]

Powder X-ray diffraction was conducted under the measurement conditions similar to those in 4. (powder X-ray diffraction) of Test Examples 3. The temperature was increased according to the following conditions.

Temperature controller: PCT-20 (manufactured by Rigaku Denki KK)

Rate for the increase of the temperature: 2 °C/min

Measurement temperatures: 30 °C, 40 °C, 60 °C, 80 °C, 120 °C, 140 °C, 180 °C, 200 °C, 205 °C, 210 °C and 215 °C.

[Results]

While crystal transition was not observed at temperatures from 30 °C to 80 °C, at temperatures of 120 °C or more transition to a crystalline form of the mesylate (Form C) was observed.

[0088] (Powder X-ray diffraction measurement)

Powder X-ray diffraction analysis was carried out for crystals obtained in Preparation Example 1 and Examples 1, 2, 3, 4, 5, 6, 7, 9, 10, 11 and 12 under the following measurement conditions in accordance with "X-Ray Powder Diffraction Method" described in Japanese Pharmacopoeia 14th Edition, General Tests (B-614 to 619).

Apparatus: RINT-2000 (manufactured by Rigaku Denki KK)

X-ray: CuKα ray

Monochrometer: curved crystal monochrometer

Goniometer: vertical goniometer

Counter: scintillation counter

Applied voltage: 40 kV

Charging current: 200 mA

Scan speed: 5°/min (2°/min with respect to a crystalline form of the free form of the carboxamide obtained in Preparation Example 1, a crystalline form of the hydrochloride obtained in Example 1, a crystalline form of the hydrobromide obtained in Example 2, and a crystalline form of the acetic acid solvate of the mesylate (Form I) obtained in Example 10)

Scan axis: 2θ/θ

Scan range: 2θ = 5 to 40°

Divergent slit: 0.5°

Scattering slit: 0.5°

Receiving slit: 0.3 mm

[0089] The powder X-ray diffraction patterns of the crystals obtained in Preparation Example 1 and Examples 1, 2, 3, 4, 5, 6, 7, 9, 10, 11 and 12 are shown in Figs. 2 to 13, respectively. The peaks and intensities of the diffraction angles (2θ) for the crystals obtained in Preparation Example 1 and Examples 5, 6, 7, 9, 10, 11 and 12 are listed in Tables 12 to 19, respectively.

[0090] [Table 12]

PEAK NUMBER	2θ	HALF WIDTH	d_VALUE	INTENSITY	RELATIVE INTENSITY	PEAK NUMBER	2θ	HALF WIDTH	d_VALUE	INTENSITY	RELATIVE INTENSITY
1	7.210	0.165	12.2505	1593	7	31	27.710	0.176	3.2167	2077	9
2	8.250	0.153	10.7084	4113	18	32	28.010	0.141	3.1829	1190	5
3	8.930	0.176	9.8944	1680	7	33	28.560	0.188	3.1228	4867	22
4	9.200	0.141	9.6046	1710	8	34	28.860	0.165	3.0911	3810	17
5	9.910	0.165	8.9180	3680	16	35	29.400	0.212	3.0355	2050	9
6	10.430	0.188	8.4746	2220	10	36	30.490	0.188	2.9294	6207	28
7	10.930	0.153	8.0880	4197	19	37	30.880	0.247	2.8933	2667	12
8	12.240	0.188	7.2251	1853	8	38	31.280	0.188	2.8572	1397	6
9	13.720	0.165	6.4489	6133	27	39	31.760	0.259	2.8151	3050	14
10	15.090	0.165	5.8664	2283	10	40	32.100	0.176	2.7861	1447	6
11	15.370	0.141	5.7601	2553	11	41	32.920	0.129	2.7185	1310	6
12	15.700	0.176	5.6398	7390	33	42	33.120	0.212	2.7026	1597	7
13	16.550	0.188	5.3520	1293	6	43	33.710	0.141	2.6566	1337	6
14	18.580	0.176	4.7716	9897	44	44	34.290	0.259	2.6130	1163	5
15	19.230	0.188	4.6117	15977	71	45	34.640	0.165	2.5874	1223	5
16	19.930	0.165	4.4513	4683	21	46	34.940	0.188	2.5658	1350	6
17	20.330	0.188	4.3646	13577	60	47	36.080	0.176	2.4873	1117	5
18	20.970	0.176	4.2328	3610	16	48	36.730	0.176	2.4448	2140	10
19	22.010	0.176	4.0351	3100	14	49	37.600	0.235	2.3902	1677	7
20	22.410	0.259	3.9640	5203	23	50	38.140	0.188	2.3576	1500	7
21	22.970	0.165	3.8686	2593	12	51	38.600	0.212	2.3306	1200	5
22	23.440	0.188	3.7921	22513	100	52	39.400	0.271	2.2851	1650	7
23	24.110	0.176	3.6882	5120	23						
24	24.540	0.176	3.6245	5353	24						
25	24.990	0.188	3.5603	5263	23						
26	25.520	0.188	3.4875	1857	8						
27	25.790	0.141	3.4516	1370	6						
28	26.280	0.188	3.3884	8420	37						
29	26.880	0.188	3.3141	4030	18						
30	27.400	0.176	3.2524	2080	9						

[0091] [Table 13]

PEAK NUMBER	2θ	HALF WIDTH	d_VALUE	INTENSITY	RELATIVE INTENSITY	PEAK NUMBER	2θ	HALF WIDTH	d_VALUE	INTENSITY	RELATIVE INTENSITY
1	6.540	0.188	13.5039	1954	10	31	26.740	0.188	3.3311	3558	19
2	9.660	0.141	9.1483	9646	52	32	27.060	0.141	3.2924	1192	6
3	10.640	0.188	8.3078	2562	14	33	27.640	0.212	3.2247	2842	15
4	11.380	0.141	7.7692	3025	16	34	28.320	0.212	3.1488	1812	10
5	12.220	0.212	7.2369	1592	9	35	28.600	0.141	3.1186	1892	10
6	12.640	0.141	6.9974	1808	10	36	29.220	0.165	3.0538	1746	9
7	13.100	0.165	6.7527	1917	10	37	29.680	0.141	3.0075	3154	17
8	14.480	0.141	6.1121	1904	10	38	29.960	0.188	2.9800	5300	28
9	15.020	0.165	5.8935	1304	7	39	30.300	0.165	2.9474	1846	10
10	15.420	0.212	5.7415	1600	9	40	31.800	0.118	2.8117	1412	8
11	16.740	0.165	5.2917	3446	18	41	32.660	0.212	2.7396	2133	11
12	17.020	0.165	5.2052	1704	9	42	32.940	0.141	2.7169	1567	8
13	17.300	0.141	5.1216	2129	11	43	33.360	0.259	2.6837	1312	7
14	17.700	0.165	5.0068	2329	12	44	35.400	0.141	2.5335	1867	10
15	18.380	0.165	4.8230	3825	20	45	36.660	0.235	2.4493	1167	6
16	18.880	0.165	4.6964	3479	19	46	37.240	0.259	2.4125	1412	8
17	19.400	0.235	4.5717	2800	15	47	38.320	0.165	2.3469	1575	8
18	19.960	0.165	4.4447	4054	22	48	38.700	0.118	2.3248	1425	8
19	20.340	0.141	4.3625	4133	22						
20	20.820	0.235	4.2630	10558	56						
21	21.380	0.165	4.1526	5504	29						
22	22.180	0.188	4.0046	4988	27						
23	22.900	0.165	3.8803	5158	28						
24	23.180	0.141	3.8340	9562	51						
25	23.420	0.165	3.7953	18721	100						
26	24.080	0.141	3.6927	2438	13						
27	24.820	0.188	3.5843	3908	21						
28	25.480	0.212	3.4929	3183	17						
29	25.880	0.212	3.4398	2012	11						
30	26.400	0.141	3.3732	2288	12						

[0092] [Table 14]

PEAK NUMBER	2θ	HALF WIDTH	d_VALUE	INTENSITY	RELATIVE INTENSITY	PEAK NUMBER	2θ	HALF WIDTH	d_VALUE	INTENSITY	RELATIVE INTENSITY
1	5.720	0.141	15.4378	3079	45	31	33.560	0.118	2.6681	1671	24
2	9.640	0.165	9.1672	2229	33	32	34.440	0.141	2.6019	1267	19
3	10.140	0.188	8.7163	2788	41						
4	10.500	0.235	8.4182	2458	36						
5	11.320	0.212	7.8102	4175	61						
6	11.480	0.141	7.7017	4042	59						
7	13.260	0.118	6.6716	1550	23						
8	13.840	0.212	6.3933	3333	49						
9	15.280	0.165	5.7938	1862	27						
10	15.620	0.188	5.6685	1508	22						
11	16.440	0.212	5.3875	1488	22						
12	17.060	0.165	5.1931	2154	32						
13	17.620	0.259	5.0293	4746	69						
14	19.160	0.212	4.6284	6829	100						
15	19.800	0.235	4.4802	2896	42						
16	20.340	0.282	4.3625	2279	33						
17	20.760	0.212	4.2752	2079	30						
18	21.460	0.188	4.1373	2558	37						
19	22.080	0.259	4.0225	1871	27						
20	22.560	0.118	3.9380	2292	34						
21	23.140	0.141	3.8406	3012	44						
22	23.840	0.306	3.7293	3167	46						
23	24.940	0.353	3.5673	3958	58						
24	25.780	0.212	3.4529	3571	52						
25	26.800	0.118	3.3238	1458	21						
26	28.300	0.118	3.1509	2029	30						
27	29.900	0.165	2.9859	1683	25						
28	31.040	0.118	2.8788	1467	21						
29	31.160	0.118	2.8679	1379	20						
30	32.760	0.165	2.7314	1429	21						

[0093] [Table 15]

PEAK NUMBER	2θ	HALF WIDTH	d_VALUE	INTENSITY	RELATIVE INTENSITY	PEAK NUMBER	2θ	HALF WIDTH	d_VALUE	INTENSITY	RELATIVE INTENSITY
1	6.160	0.141	14.3361	3760	37	31	26.020	0.141	3.4216	2278	23
2	9.840	0.165	8.9813	3062	31	32	26.220	0.118	3.3960	1422	14
3	10.160	0.165	8.6992	3238	32	33	26.980	0.212	3.3020	2438	24
4	10.580	0.141	8.3547	7715	77	34	27.500	0.165	3.2408	1085	11
5	12.300	0.141	7.1900	1923	19	35	27.980	0.235	3.1862	1798	18
6	12.540	0.118	7.0530	1783	18	36	28.400	0.212	3.1401	2785	28
7	12.960	0.141	6.8253	1912	19	37	28.760	0.141	3.1016	1137	11
8	13.400	0.141	6.6022	1655	16	38	29.220	0.212	3.0538	1517	15
9	14.220	0.212	6.2233	3978	40	39	29.500	0.118	3.0254	1727	17
10	14.860	0.188	5.9566	1905	19	40	29.620	0.165	3.0134	1818	18
11	15.200	0.165	5.8241	3047	30	41	29.840	0.118	2.9917	1643	16
12	15.960	0.235	5.5485	1383	14	42	30.640	0.376	2.9154	2390	24
13	16.360	0.212	5.4137	1267	13	43	31.280	0.259	2.8572	1123	11
14	17.160	0.141	5.1631	1793	18	44	31.500	0.118	2.8378	1062	11
15	17.600	0.282	5.0350	4173	42	45	32.440	0.141	2.7576	1100	11
16	19.080	0.165	4.6476	6007	60	46	33.640	0.118	2.6620	1208	12
17	19.280	0.165	4.5999	5716	57	47	34.500	0.165	2.5976	1362	14
18	19.960	0.188	4.4447	4740	47	48	35.040	0.118	2.5587	1297	13
19	20.420	0.165	4.3456	2607	26	49	36.100	0.188	2.4860	1245	12
20	20.820	0.212	4.2630	3305	33	50	37.640	0.306	2.3878	1565	16
21	21.280	0.188	4.1719	3210	32	51	38.940	0.141	2.3110	1427	14
22	21.740	0.235	4.0846	4487	45	52	39.480	0.118	2.2806	1215	12
23	22.560	0.282	3.9380	3627	36						
24	23.140	0.188	3.8406	2402	24						
25	23.560	0.188	3.7730	10033	100						
26	23.720	0.118	3.7479	6733	67						
27	24.020	0.141	3.7018	5015	50						
28	24.320	0.259	3.6568	4275	43						
29	24.760	0.259	3.5928	2563	26						
30	25.540	0.282	3.4848	8082	81						

[0094] [Table 16]

PEAK NUMBER	2θ	HALF WIDTH	d_VALUE	INTENSITY	RELATIVE INTENSITY
1	5.700	0.212	15.4919	1821	25
2	6.100	0.188	14.4770	1946	26
3	8.020	0.212	11.0149	4092	56
4	9.640	0.212	9.1672	2379	32
5	10.540	0.165	8.3864	2021	27
6	11.280	0.259	7.8378	3871	53
7	12.680	0.236	6.9754	2129	29
8	14.140	0.259	6.2583	1358	18
9	16.120	0.212	5.4938	1529	21
10	17.200	0.259	5.1512	2258	31
11	18.140	0.235	4.8863	5121	70
12	19.620	0.235	4.5209	3671	50
13	20.240	0.165	4.3838	1921	26
14	20.700	0.329	4.2874	2962	40
15	21.320	0.235	4.1641	1525	21
16	22.120	0.212	4.0153	2558	35
17	22.900	0.282	3.8803	5721	78
18	23.400	0.188	3.7985	4458	61
19	23.740	0.259	3.7448	5092	69
20	24.280	0.259	3.6628	3929	53
21	24.760	0.188	3.5928	1971	27
22	25.060	0.235	3.5505	2154	29
23	25.500	0.282	3.4902	2454	33
24	26.300	0.282	3.3858	2083	28
25	26.960	0.329	3.3044	7362	100
26	28.300	0.212	3.1509	1921	26
27	28.820	0.306	3.0953	1850	25
28	29.480	0.329	3.0274	2371	32
29	29.920	0.165	2.9839	1554	21
30	31.660	0.353	2.8238	1321	18
31	34.840	0.259	2.5730	1700	23
32	36.280	0.329	2.4741	1888	26
33	37.940	0.165	2.3696	1400	19

[0095] [Table 17]

PEAK NUMBER	2θ	HALF WIDTH	d_VALUE	INTENSITY	RELATIVE INTENSITY	PEAK NUMBER	2θ	HALF WIDTH	d_VALUE	INTENSITY	RELATIVE INTENSITY
1	9.360	0.188	9.4408	6027	100	31	31.640	0.118	2.8255	960	16
2	10.200	0.165	8.6651	2107	35	32	32.520	0.141	2.7510	1057	18
3	10.460	0.165	8.4503	3292	55	33	33.340	0.212	2.6852	1740	29
4	12.400	0.165	7.1323	2693	45	34	35.120	0.118	2.5531	985	16
5	13.380	0.188	6.6120	1382	23	35	35.440	0.141	2.5308	953	16
6	13.880	0.235	6.3749	1450	24	36	35.860	0.165	2.5021	937	16
7	14.400	0.165	6.1459	1432	24	37	37.360	0.259	2.4050	1443	24
8	15.640	0.282	5.6613	3673	61	38	39.560	0.141	2.2762	1217	20
9	16.840	0.165	5.2605	1560	26						
10	17.260	0.118	5.1334	2425	40						
11	17.460	0.165	5.0750	4155	69						
12	18.860	0.212	4.7014	2442	40						
13	19.420	0.212	4.5670	1597	26						
14	20.040	0.212	4.4271	2845	47						
15	20.760	0.212	4.2752	3693	61						
16	21.100	0.212	4.2070	2805	46						
17	21.760	0.188	4.0809	6035	100						
18	22.660	0.212	3.9208	3982	66						
19	23.200	0.188	3.8308	1322	22						
20	23.660	0.212	3.7573	4177	69						
21	25.180	0.329	3.5338	4802	80						
22	25.660	0.188	3.4688	3073	51						
23	25.840	0.141	3.4451	2603	43						
24	26.480	0.188	3.3632	1992	33						
25	26.980	0.235	3.3020	2142	35						
26	28.040	0.329	3.1796	2292	38						
27	28.480	0.118	3.1314	995	16						
28	29.740	0.282	3.0016	1248	21						
29	30.360	0.282	2.9417	1915	32						
30	31.200	0.188	2.8644	1075	18						

[0096] [Table 18]

PEAK NUMBER	2θ	HALF WIDTH	d_VALUE	INTENSITY	RELATIVE INTENSITY	PEAK NUMBER
1	6.000	0.188	14.7180	2058	37	
2	9.200	0.447	9.6046	2108	38	
3	10.640	0.235	8.3078	5392	96	
4	13.480	0.165	6.5632	1862	33	
5	13.620	0.165	6.4960	1783	32	
6	14.520	0.212	6.0953	1946	35	
7	15.700	0.259	5.6398	2775	49	
8	17.180	0.282	5.1571	2508	45	
9	17.820	0.282	4.9733	2579	46	
10	18.380	0.259	4.8230	2571	46	
11	19.880	0.306	4.4624	4421	79	
12	20.720	0.259	4.2833	2712	48	
13	21.460	0.518	4.1373	2692	48	
14	22.200	0.259	4.0010	3658	65	
15	22.820	0.471	3.8937	5621	100	
16	24.160	0.165	3.6807	2438	43	
17	24.600	0.282	3.6158	2942	52	
18	25.560	0.306	3.4822	4200	75	
19	26.200	0.188	3.3985	1667	30	
20	26.900	0.353	3.3117	2196	39	
21	27.180	0.165	3.2782	1854	33	
22	28.220	0.353	3.1597	2212	39	
23	29.320	0.353	3.0436	1696	30	
24	30.260	0.212	2.9512	1721	31	

[0097] [Table 19]

PEAK NUMBER	2θ	HALF WIDTH	d_VALUE	INTENSITY	RELATIVE INTENSITY	PEAK NUMBER	2θ	HALF WIDTH	d_VALUE	INTENSITY	RELATIVE INTENSITY
1	6.480	0.165	13.6288	2662	20	31	26.740	0.188	3.3311	3650	27
2	9.040	0.141	9.7743	5021	38	32	27.260	0.188	3.2687	5421	41
3	9.580	0.141	9.2245	10096	76	33	27.480	0.141	3.2431	3008	23
4	10.600	0.118	8.3390	2671	20	34	28.360	0.165	3.1444	1767	13
5	12.500	0.141	7.0754	2096	16	35	28.580	0.141	3.1207	1267	10
6	13.660	0.141	6.4771	1558	12	36	29.300	0.141	3.0456	1404	11
7	14.640	0.212	6.0456	1712	13	37	29.560	0.212	3.0194	2117	16
8	15.080	0.141	5.8702	7054	53	38	30.360	0.212	2.9417	2275	17
9	17.740	0.235	4.9956	2675	20	39	30.860	0.188	2.8951	2250	17
10	18.140	0.165	4.8863	4188	32	40	31.860	0.141	2.8065	1392	10
11	19.100	0.141	4.6428	3083	23	41	32.140	0.118	2.7827	1204	9
12	19.400	0.212	4.5717	6029	45	42	33.600	0.259	2.6650	1779	13
13	19.700	0.141	4.5027	2796	21	43	35.360	0.141	2.5363	1800	14
14	20.080	0.141	4.4184	2862	22	44	35.580	0.141	2.5211	1408	11
15	20.380	0.141	4.3540	3279	25	45	36.360	0.141	2.4688	1896	14
16	20.660	0.165	4.2956	10933	82	46	36.740	0.118	2.4442	1650	12
17	20.920	0.141	4.2428	2729	21	47	37.520	0.235	2.3951	1650	12
18	21.280	0.118	4.1719	2771	21	48	38.180	0.235	2.3552	1471	11
19	21.520	0.165	4.1259	6142	46	49	38.900	0.235	2.3133	2033	15
20	21.740	0.141	4.0846	4908	37	50	39.640	0.118	2.2718	1500	11
21	22.140	0.165	4.0117	3754	28						
22	22.680	0.165	3.9174	13275	100						
23	23.220	0.165	3.8275	2008	15						
24	23.640	0.188	3.7604	6554	49						
25	24.260	0.165	3.6657	5350	40						
26	24.880	0.165	3.5758	3129	24						
27	25.160	0.141	3.5366	2350	18						
28	25.320	0.118	3.5146	1879	14						
29	26.100	0.165	3.4113	4004	30						
30	26.260	0.141	3.3909	3646	27						

[0098] (^{13}C Solid State NMR spectrum measurement)

^{13}C Solid State NMR spectrum measurement was carried out for crystals obtained in Examples 5 and 7 under the following measurement conditions.

Apparatus: CMX-300 (Chemagnetics)

Measurement temperature: room temperature (22 °C)

Chemical shift reference: poly(dimethylsiloxane) (Internal Standard: 1.56 ppm)

Measurement nucleus: ^{13}C (75.497791MHz)

Relaxation delay: 25 sec

Pulse sequence: TOSS

[0099] The ^{13}C Solid State NMR spectra of the crystals obtained in Examples 5 and 7 are shown in Fig. 14 and Fig. 15, respectively. The chemical shifts of the crystals obtained in Examples 5 and 7 are listed in Tables 20 and 21, respectively.

[0100] [Table 20]

mesylate (Form A)
chemical shift (ppm)
169.7
162.4
156.3
147.5
142.3
137.0
130.1
128.0
123.4
120.5
114.6
102.3
98.4
58.8
39.2
23.8
9.9
5.7

[0101] [Table 21]

mesylate (Form C)
chemical shift (ppm)
170.9
166.1
160.2
155.3
148.1
144.6
142.4
136.8
130.3
126.6
122.9
121.4
115.9
105.6
97.0
57.4
39.3
21.9
7.8

[0102] (Infrared absorption spectrum measurement)

Infrared absorption spectrum measurement was carried out for crystals obtained in Examples 5, 6, 7, 10, 11 and 12 was carried out according to the ATR method in the infrared absorption spectrum method as described in the Japanese Pharmacopoeia 14th Edition, General Tests by using FT-IR Spectrum-One (manufactured by PerkinElmer Japan Co., Ltd.) with a measurement range of 4000-400 cm^{-1} and a resolution of 4 cm^{-1}.

[0103] The infrared absorption spectra of the crystals obtained in Examples 5, 6, 7, 10, 11 and 12 are shown in Figs. 16 to 21, respectively, and wave numbers of the absorption peaks (cm^{-1}) and transmittance (%T) are listed in Tables 22 to 27, respectively.

[0104] [Table 22]

MESYLATE (FORM A)							
WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T
3306.50	87.76	1350.26	72.77	846.45	83.06	523.19	63.87
3143.87	89.68	1311.98	88.26	827.77	76.51	458.48	77.37
2676.03	90.20	1280.50	77.49	811.59	76.37	428.43	84.18
2179.21	92.50	1239.62	73.06	775.98	73.68	404.39	73.43
1709.03	76.99	1204.43	65.76	756.07	82.42		
1689.20	75.28	1194.13	65.42	739.83	85.42		
1639.51	83.49	1181.63	65.44	721.85	79.51		
1589.27	83.46	1161.34	62.76	697.83	84.41		
1526.06	76.88	1091.07	79.89	681.20	81.05		
1492.40	85.76	1044.40	60.26	642.73	72.54		
1456.75	74.01	985.56	78.02	595.47	76.50		
1420.18	83.16	911.30	76.39	550.94	56.67		

[0105] [Table 23]

MESYLATE (FORM B)							
WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T
3403.30	88.90	1447.27	70.65	1034.51	53.11	621.03	80.63
3288.86	87.65	1418.76	72.95	988.08	74.83	582.94	68.34
3148.98	86.30	1385.12	68.18	957.18	82.10	553.10	54.69
2500.86	89.65	1349.46	74.29	917.63	74.99	524.26	52.32
2071.00	90.59	1281.22	76.13	885.07	76.41	460.20	71.59
1975.82	90.44	1259.90	66.26	846.37	75.01	445.97	70.23
1676.34	72.60	1238.09	73.20	824.56	71.62	429.58	74.11
1654.00	75.28	1216.34	65.61	774.19	68.81	417.86	77.33
1610.72	80.67	1187.31	65.81	740.35	79.48	404.47	75.14
1585.16	80.02	1147.23	59.40	717.65	83.13		
1549.95	76.15	1086.20	72.28	697.26	75.94		
1492.04	71.57	1068.05	78.63	667.94	76.40		
1474.49	78.84	1051.40	77.11	648.45	76.93		

[0106] [Table 24]

MESYLATE (FORM C)							
WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T
3423.95	95.31	1454.93	79.66	1053.79	88.07	678.66	86.22
3387.99	94.61	1417.85	85.41	1031.32	69.48	622.21	83.97
3265.37	94.09	1390.53	79.57	999.13	86.02	599.75	82.04
3134.95	93.21	1352.31	83.39	957.03	92.45	589.04	82.04
2189.73	96.49	1323.76	82.35	923.13	91.37	578.57	84.66
2055.55	96.35	1286.71	83.52	909.07	83.03	553.91	71.59
1701.76	86.67	1259.58	78.08	885.46	87.22	522.49	56.69
1682.83	77.44	1241.58	83.13	873.44	88.13	502.44	71.80
1652.89	90.15	1211.19	71.92	849.08	79.00	456.20	76.23
1613.76	88.25	1185.21	72.85	823.54	86.89	446.12	77.77
1587.67	89.60	1151.72	68.76	770.37	80.47	419.73	79.39
1528.85	75.23	1132.10	77.56	746.03	83.64		
1474.24	89.39	1094.87	80.65	720.92	92.81		

[0107] [Table 25]

MESYLATE (FORM I)							
WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T
3397.97	86.39	1505.67	75.91	1057.74	71.52	601.50	59.64
3319.94	84.81	1474.53	73.63	1030.17	53.75	547.68	44.53
3177.53	83.45	1453.55	63.44	989.94	65.62	526.55	45.99
3096.06	83.80	1416.08	65.42	971.08	73.93	482.62	58.93
2159.87	91.01	1396.67	60.87	909.73	61.10	471.45	60.44
2032.91	90.61	1350.85	66.67	876.69	74.65	444.14	59.99
1749.63	86.77	1284.69	68.19	844.04	65.31	423.38	58.76
1724.72	86.69	1260.86	62.02	798.03	71.63		
1683.59	71.59	1223.56	52.48	772.20	68.51		
1641.48	62.67	1201.48	57.53	717.29	75.90		
1605.84	67.15	1186.05	55.01	686.79	66.91		
1585.45	65.70	1146.06	51.51	668.46	68.22		
1557.92	64.45	1091.15	69.64	650.21	68.04		

[0108] [Table 26]

ESYLATE (FORM α)							
WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T
3422.06	93.12	1385.04	83.40	931.15	91.11	527.37	71.96
3303.44	89.24	1355.81	74.56	909.24	84.55	514.22	64.33
3128.13	92.01	1319.88	77.31	885.60	88.76	476.26	89.39
2595.94	92.67	1296.55	77.66	872.37	82.05	460.92	87.09
2276.37	95.87	1253.87	64.28	838.72	77.28	446.30	84.63
2051.39	95.50	1199.61	71.21	779.73	90.55	429.94	87.20
1694.09	72.13	1187.91	69.92	741.49	76.67	416.02	78.03
1644.75	84.09	1139.76	64.85	723.87	81.99		
1588.32	83.16	1092.92	83.86	676.10	84.75		
1529.21	65.27	1066.96	88.29	599.47	91.23		
1457.83	69.69	1055.19	86.48	578.37	80.13		
1426.95	85.03	1028.72	62.50	552.44	80.28		
1400.48	72.09	996.79	86.93	537.09	74.86		

[0109] [Table 27]

ESYLATE (FORM β)							
WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T	WAVE NUMBER (cm^{-1})	%T
3303.18	78.44	1426.27	66.22	1033.17	38.75	612.89	65.29
3107.11	84.00	1398.05	55.56	985.47	65.92	591.48	61.15
3000.63	87.00	1355.93	50.43	945.83	78.73	578.14	47.06
2931.74	88.33	1309.97	80.04	910.85	56.84	551.71	51.97
2582.21	87.39	1281.20	64.46	892.18	69.98	529.84	43.75
2260.15	91.52	1241.00	51.31	871.99	76.39	518.10	46.42
2040.56	90.88	1205.77	45.41	840.95	59.27	468.69	66.48
1968.01	91.72	1184.19	43.37	830.58	55.72	457.49	62.27
1689.52	55.42	1151.28	55.33	788.17	78.25	446.73	65.90
1647.24	71.29	1131.31	44.71	763.00	78.08	430.38	71.60
1587.52	70.97	1086.08	65.79	741.34	50.54	405.91	50.91
1524.38	57.93	1061.38	70.95	682.32	67.23		
1453.72	46.32	1049.91	62.19	644.25	70.08		

[0110] (Preparation of pharmaceutical composition)

1 mg tablet

24 g of a crystalline form of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide methanesulfonate (Form C) (hereunder, referred to as "Crystalline Form C") and 192 g of light anhydrous silicic acid (anti-gelation agent; trade name: Aerosil (registered trademark) 200, Nippon Aerosil Co., Ltd.) were mixed using a 20 L super mixer, after which 1236 g of D-mannitol (excipient; Towa Chemical Industry Co., Ltd.), 720 g of crystalline cellulose (excipient; trade name: Avicel PH 101, Asahi Chemical Industry Co., Ltd.) and 72 g of hydroxypropylcellulose (binder; trade name: HPC-L, Nippon Soda Co., Ltd.) were further added and mixed. Thereafter, a suitable amount of anhydrous ethanol was added to produce granulated products containing Crystalline Form C. The granulated products were dried with a shelf dryer (60 °C), and size-controlled using a power mill to produce granules. The obtained granules were mixed in a 20 L tumbler mixer with 120 g of croscarmellose sodium (disintegrator; trade name: Ac-Di-Sol, FMC International Inc.) and 36 g of sodium stearyl fumarate (lubricant; JRS Pharma LP), and the resulting mixture was formed into tablets with a tableting machine to produce tablets having a total weight of 100 mg. These tablets were then coated using a tablet coating machine employing a 10% aqueous solution of opadry yellow (opadry 03F42069 yellow, Colorcon (Japan) Ltd.) as a coating solution, to produce coated tablets having a total weight of 105 mg.

[0111] 10 mg tablet

60 g of Crystalline Form C and 192 g of light anhydrous silicic acid (anti-gelation agent; trade name: Aerosil (registered trademark) 200, Nippon Aerosil Co., Ltd.) were mixed using a 20 L super mixer, after which 1200 g of D-mannitol (excipient; Towa Chemical Industry Co., Ltd.), 720 g of crystalline cellulose (excipient; trade name: Avicel PH 101, Asahi Chemical Industry Co., Ltd.) and 72 g of hydroxypropylcellulose (binder; trade name: HPC-L, Nippon Soda Co., Ltd.) were further added and mixed. Thereafter, a suitable amount of anhydrous ethanol was added to produce

granulated products containing Crystalline Form C. The granulated products were dried with a shelf dryer (60 °C), and size-controlled using a power mill to produce granules. The obtained granules were mixed in a 20 L tumbler mixer with 120 g of croscarmellose sodium (disintegrator; trade name: Ac-Di-Sol, FMC International Inc.) and 36 g of sodium stearyl fumarate (lubricant; JRS Pharma LP), and the resulting mixture was formed into tablets with a tableting machine to produce tablets having a total weight of 400 mg. These tablets were then coated using a tablet coating machine employing a 10% aqueous solution of opadry yellow (opadry 03F42069 yellow, Colorcon (Japan) Ltd.) as a coating solution, to produce coated tablets having a total weight of 411 mg.

[0112] 100 mg tablet

31.4 g of Crystalline Form C and 4 g of light anhydrous silicic acid (anti-gelation agent; trade name: Aerosil (registered trademark) 200, Nippon Aerosil Co., Ltd.) were mixed using a 1 L super mixer, after which 40.1 g of anhydrous dibasic calcium phosphate (excipient; Kyowa Chemical Industry Co., Ltd.), 10 g of low-substituted hydroxypropylcellulose (binder; trade name: L-HPC (LH-21), Shin-Etsu Chemical Co., Ltd.) and 3 g of hydroxypropylcellulose (binder; trade name: HPC-L, Nippon Soda Co., Ltd.) were further added and mixed. Thereafter, a suitable amount of anhydrous ethanol was added thereto to produce granulated products containing Crystalline Form C. The granulated products were dried with a shelf dryer (60 °C), and size-controlled using a power mill to produce granules. The obtained granules were mixed with 10 g of croscarmellose sodium (disintegrator; trade name: Ac-Di-Sol, FMC International Inc.) and 1.5 g of sodium stearyl fumarate (lubricant; JRS Pharma LP), and the resulting mixture was formed into tablets with a tableting machine to produce tablets having a total weight of 400 mg.

Industrial Applicability

[0113] The salt of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide, the solvate of the salt as well as the crystalline form thereof according to the present invention have excellent characteristics in

terms of physical properties and pharmacokinetics, and are extremely useful as an angiogenesis inhibitor or a c-Kit kinase inhibitor.